



**Clinical trial results:**

**Phase II biomarker study evaluating the upfront combination of BRAF inhibitor dabrafenib with MEK inhibitor trametinib versus the combination after eight weeks of monotherapy with dabrafenib or trametinib in patients with metastatic and unresectable stage III or IV melanoma harbouring an activating BRAF mutation**

**Summary**

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2012-004577-12  |
| Trial protocol           | ES              |
| Global end of trial date | 19 January 2017 |

**Results information**

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1              |
| This version publication date  | 27 January 2018 |
| First version publication date | 27 January 2018 |

**Trial information**

**Trial identification**

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 116613 |
|-----------------------|--------|

**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:

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**Results analysis stage**

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|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 23 March 2017 |
| Is this the analysis of the primary completion data? | No            |

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|                                  |                 |
|----------------------------------|-----------------|
| Global end of trial reached?     | Yes             |
| Global end of trial date         | 19 January 2017 |
| Was the trial ended prematurely? | Yes             |

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Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate biomarkers linked to treatment response, resistance and toxicity including skin toxicity when dabrafenib and trametinib combination is given upfront or as monotherapy before the combination treatment.

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Protection of trial subjects:

At the time the study was early terminated, subjects who were still receiving clinical benefit and based on the discretion of the Investigator had the option to continue treatment through Sponsor established programs in the local country

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Background therapy: -

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Evidence for comparator: -

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|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 13 November 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 37 |
| Country: Number of subjects enrolled | Spain: 11  |
| Worldwide total number of subjects   | 48         |
| EEA total number of subjects         | 48         |

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Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 33 |
| From 65 to 84 years                       | 14 |
| 85 years and over                         | 1  |

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## Subject disposition

### Recruitment

Recruitment details:

This is an open label, randomized, phase II study to compare the combination of dabrafenib with trametinib versus the combination after eight weeks of monotherapy with dabrafenib or trametinib in metastatic and unresectable stage III or IV melanoma. The study was terminated early due to slow enrollment and limited numbers of viable tissue samples.

### Pre-assignment

Screening details:

This study was planned to enroll 54 participants randomized in 1:1:1 ratio into the three treatment arms; dabrafenib followed by combination therapy, trametinib followed by combination therapy and only combination therapy. The study was early terminated with 48 participants enrolled.

### Period 1

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

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Dabrafenib followed by combination therapy |

Arm description:

Eligible participants received dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.

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

Dosage and administration details:

Dabrafenib was given as an oral capsule with a dose of 150 mg twice a day (BID).

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Trametinib         |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Trametinib was given as an oral film-coated tablet with a dose of 2 milligrams (mg) once daily.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Trametinib followed by combination therapy |
|------------------|--|

Arm description:

Eligible participants received trametinib 2 mg per day continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.

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

Dosage and administration details:

Dabrafenib was given as an oral capsule with a dose of 150 mg twice a day (BID).

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Trametinib         |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Trametinib was given as an oral film-coated tablet with a dose of 2 milligrams (mg) once daily.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Combination therapy |
|------------------|---------------------|

Arm description:

Eligible participants received trametinib 2 mg per day plus dabrafenib 150 mg BID continuously until disease progression, death or unacceptable toxicity.

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

Dosage and administration details:

Dabrafenib was given as an oral capsule with a dose of 150 mg twice a day (BID).

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Trametinib         |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Trametinib was given as an oral film-coated tablet with a dose of 2 milligrams (mg) once daily.

| Number of subjects in period 1  | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |
|---------------------------------|--|--|---------------------|
|                                 |  |  |                     |
| Started                         | 16   | 16   | 16                  |
| Completed                       | 8  | 6  | 7                   |
| Not completed                   | 8  | 10   | 9                   |
| Physician decision              | 2  | 1  | -                   |
| Consent withdrawn by subject    | 1  | -  | 1                   |
| Adverse event, non-fatal        | -  | 6  | 4                   |
| Other (Study Closed/Terminated) | 5  | 3  | 4                   |

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | Dabrafenib followed by combination therapy |
| Reporting group description:<br>Eligible participants received dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity. |  |
| Reporting group title  | Trametinib followed by combination therapy |
| Reporting group description:<br>Eligible participants received trametinib 2 mg per day continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.                          |  |
| Reporting group title  | Combination therapy                        |
| Reporting group description:<br>Eligible participants received trametinib 2 mg per day plus dabrafenib 150 mg BID continuously until disease progression, death or unacceptable toxicity.  |  |

| Reporting group values             | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |
|------------------------------------|--|--|---------------------|
| Number of subjects                 | 16   | 16   | 16                  |
| Age categorical<br>Units: Subjects |  |  |                     |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 56.6<br>± 16.43 | 56.5<br>± 11.77 | 58.9<br>± 13.55 |
| Gender categorical<br>Units: Subjects                                   |                 |                 |                 |
| Female  | 7               | 8               | 6               |
| Male  | 9               | 8               | 10              |
| Race/Ethnicity, Customized<br>Units: Subjects                           |                 |                 |                 |
| Asian-South East Asian Heritage   | 0               | 1               | 0               |
| White - White/Caucasian/European  | 16              | 15              | 16              |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 48    |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|   |   |  |  |
|---|---|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | - |  |  |
| Gender categorical<br>Units: Subjects                                   |   |  |  |

|        |    |  |  |
|--------|----|--|--|
| Female | 21 |  |  |
| Male   | 27 |  |  |

|   |    |  |  |
|---|----|--|--|
| Race/Ethnicity, Customized<br>Units: Subjects |    |  |  |
| Asian-South East Asian Heritage               | 1  |  |  |
| White - White/Caucasian/European              | 47 |  |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Dabrafenib followed by combination therapy |
| Reporting group description:   |  |
| Eligible participants received dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity. |  |
| Reporting group title  | Trametinib followed by combination therapy |
| Reporting group description:   |  |
| Eligible participants received trametinib 2 mg per day continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.                          |  |
| Reporting group title  | Combination therapy                        |
| Reporting group description:   |  |
| Eligible participants received trametinib 2 mg per day plus dabrafenib 150 mg BID continuously until disease progression, death or unacceptable toxicity.  |  |

### Primary: Number of participants with percentage change from Baseline in extracellular signal-regulated kinase (ERK) phosphorylation (p-ERK) H score from Week 0 to Week 2

|  |  |
|--|--|
| End point title  | Number of participants with percentage change from Baseline in extracellular signal-regulated kinase (ERK) phosphorylation (p-ERK) H score from Week 0 to Week 2 <sup>[1][2]</sup> |
| End point description:   |  |
| Intra-tumoral expression levels of ERK measured using immunohistochemistry methods. A H score value ranged from 0 to a maximum score of 300 (strongest expression) was derived by summing the percentages of cells staining at each intensity multiplied by the weighted intensity of staining (0 [no staining], 1+ [weak staining], 2+ [medium staining] and 3+ [strongest staining]). Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Percentage change from Baseline was calculated by dividing change from Baseline value by Baseline value and multiplied by 100. The data has been presented for combination therapy calculated from Week 0 to Week 2. The analysis was based on the biomarker Population which included all participants with biopsy performed at screening and at least once during treatment. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| Baseline and up to 2 weeks   |  |

#### 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: There are no statistical data to report.

[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: There are no statistical data to report.

| End point values              | Combination therapy |  |  |  |
|-------------------------------|---------------------|--|--|--|
| Subject group type            | Reporting group     |  |  |  |
| Number of subjects analysed   | 5 <sup>[3]</sup>    |  |  |  |
| Units: Participants           |                     |  |  |  |
| Any Increase or No Changes    | 2                   |  |  |  |
| Any Decrease up to 80 percent | 1                   |  |  |  |
| Any Decrease > 80 percent     | 2                   |  |  |  |

Notes:

[3] - Biomarker Population

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with percentage change from Baseline in p-ERK H score from Week 8 to Week 10

|                 |   |
|-----------------|---|
| End point title | Number of participants with percentage change from Baseline in p-ERK H score from Week 8 to Week 10 <sup>[4][5]</sup> |
|-----------------|---|

End point description:

Intra-tumoral expression levels of ERK were measured using immunohistochemistry methods. A H score value ranged from 0 to a maximum score of 300 (strongest expression) was derived by summing the percentages of cells staining at each intensity multiplied by the weighted intensity of staining (0 [no staining], 1+ [weak staining], 2+ [medium staining] and 3+ [strongest staining]). Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Percentage change from Baseline was calculated by dividing change from Baseline value by Baseline value and multiplied by 100. The data has been presented for dabrafenib followed by combination therapy and trametinib followed by combination therapy, calculated from Week 8 to Week 10.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline and up to 10 weeks

Notes:

[4] - 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: There are no statistical data to report.

[5] - 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: There are no statistical data to report.

| End point values              | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy |  |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                            | Reporting group                            |  |  |
| Number of subjects analysed   | 1 <sup>[6]</sup>                           | 3 <sup>[7]</sup>                           |  |  |
| Units: Participants           |  |  |  |  |
| Any Increase or No Changes    | 1  | 1  |  |  |
| Any Decrease up to 80 percent | 0  | 1  |  |  |
| Any Decrease > 80 percent     | 0  | 1  |  |  |

Notes:

[6] - Biomarker Population

[7] - Biomarker Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with overall response rate (ORR)

|                 |   |
|-----------------|---|
| End point title | Number of participants with overall response rate (ORR) |
|-----------------|---|

End point description:

Clinical response was evaluated by ORR, which was defined as the percentage of participants with a confirmed or an unconfirmed complete response (CR) or partial response (PR) at any time per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. CR was defined as disappearance of all target lesions. PR was defined as at least a 30 percent decrease in the sum of the diameters of target lesions. Number of participants with ORR (CR+PR) has been presented. The analysis was based on the Intent-to-Treat Population (ITT) which included all the randomized participants whether or not randomized treatment was administered.

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

End point timeframe:

Up to 3.2 years

| End point values            | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|-----------------------------|--|--|---------------------|--|
| Subject group type          | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed | 16 <sup>[8]</sup>                          | 16 <sup>[9]</sup>                          | 16 <sup>[10]</sup>  |  |
| Units: Participants         |  |  |                     |  |
| Participants                | 11   | 13   | 11                  |  |

Notes:

[8] - Intent-to-Treat Population (ITT)

[9] - Intent-to-Treat Population (ITT)

[10] - Intent-to-Treat Population (ITT)

## Statistical analyses

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

The odds ratio for dabrafenib followed by combination therapy versus combination therapy has been presented.

|   |  |
|---|--|
| Comparison groups                       | Dabrafenib followed by combination therapy v Combination therapy |
| Number of subjects included in analysis | 32   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 1  |
| Method                                  | Cochran-Mantel-Haenszel  |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 1  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.224  |
| upper limit                             | 4.459  |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

The odds ratio for trametinib followed by combination therapy versus combination therapy has been presented.

|   |  |
|---|--|
| Comparison groups                       | Combination therapy v Trametinib followed by combination therapy |
| Number of subjects included in analysis | 32   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.4216   |
| Method                                  | Cochran-Mantel-Haenszel  |
| Parameter estimate                      | Odds ratio (OR)  |
| Point estimate                          | 1.97   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.382  |
| upper limit                             | 10.166   |

### Secondary: Number of participants with change in vital signs from Baseline

|  |   |
|--|---|
| End point title  | Number of participants with change in vital signs from Baseline |
| End point description:   |   |
| <p>Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured. Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus the Baseline value. The number of participants with heart rate "decrease to &lt; 60" and "increase to &gt;100" have been presented. For SBP and DBP, "any grade increase" have been presented. Any grade increase in SBP, including grade 0 (&lt;120), grade 1 (120-139), grade 2 (140-159), grade 3 (<math>\geq</math>160) and DBP including grade 0 (&lt;80), grade 1 (80-89), grade 2 (90-99), grade 3 (<math>\geq</math>100) have been presented. "99999" represents data is not available. The analysis was based on the Safety Population which included all participants who received at least one dose of randomized treatment and was based on the actual treatment received.</p> |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline and up to 3.2 years   |   |

| End point values                          | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|---|--|--|---------------------|--|
| Subject group type                        | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed               | 16 <sup>[11]</sup>                         | 16 <sup>[12]</sup>                         | 16 <sup>[13]</sup>  |  |
| Units: Participants                       |  |  |                     |  |
| HR; Week 4; Decrease to <60; n=15,16,16   | 1  | 3  | 3                   |  |
| HR; Week 4; Increase to >100; n=15,16,16  | 1  | 0  | 0                   |  |
| HR; Week 8; Decrease to <60; n=16,16,14   | 1  | 2  | 2                   |  |
| HR; Week 8; Increase to >100; n=16,16,14  | 2  | 0  | 0                   |  |
| HR; Week 12; Decrease to <60; n=16,16,13  | 2  | 1  | 2                   |  |
| HR; Week 12; Increase to >100; n=16,16,13 | 0  | 0  | 0                   |  |

|  |   |   |   |  |
|--|---|---|---|--|
| HR; Week 16; Decrease to <60;<br>n=14,16,13  | 0 | 0 | 2 |  |
| HR; Week 16; Increase to >100;<br>n=14,16,13 | 0 | 0 | 0 |  |
| HR; Week 20; Decrease to <60;<br>n=11,15,13  | 0 | 1 | 1 |  |
| HR; Week 20; Increase to >100;<br>n=11,15,13 | 1 | 1 | 0 |  |
| HR; Week 24; Decrease to <60;<br>n=12,14,13  | 1 | 2 | 2 |  |
| HR; Week 24; Increase to >100;<br>n=12,14,13 | 1 | 2 | 0 |  |
| HR; Week 28; Decrease to <60;<br>n=8,12,7    | 2 | 2 | 2 |  |
| HR; Week 28; Increase to >100;<br>n=8,12,7   | 1 | 0 | 0 |  |
| HR; Week 32; Decrease to <60;<br>n=7,11,8    | 1 | 0 | 0 |  |
| HR; Week 32; Increase to >100;<br>n=7,11,8   | 1 | 0 | 0 |  |
| HR; Week 36; Decrease to <60;<br>n=5,11,8    | 2 | 0 | 1 |  |
| HR; Week 36; Increase to >100;<br>n=5,11,8   | 0 | 0 | 1 |  |
| HR; Week 40; Decrease to <60;<br>n=6,11,7    | 1 | 1 | 0 |  |
| HR; Week 40; Increase to >100;<br>n=6,11,7   | 0 | 0 | 0 |  |
| HR; Week 44; Decrease to <60;<br>n=5,5,4     | 1 | 0 | 0 |  |
| HR; Week 44; Increase to >100;<br>n=5,5,4    | 1 | 0 | 1 |  |
| HR; Week 48; Decrease to <60;<br>n=5,4,4     | 1 | 0 | 1 |  |
| HR; Week 48; Increase to >100;<br>n=5,4,4    | 0 | 0 | 1 |  |
| HR; Week 52; Decrease to <60;<br>n=4,3,4     | 0 | 0 | 0 |  |
| HR; Week 52; Increase to >100;<br>n=4,3,4    | 0 | 0 | 1 |  |
| HR; Week 56; Decrease to <60;<br>n=4,3,4     | 1 | 0 | 3 |  |
| HR; Week 56; Increase to >100;<br>n=4,3,4    | 0 | 0 | 0 |  |
| HR; Week 60; Decrease to <60;<br>n=3,3,4     | 1 | 1 | 1 |  |
| HR; Week 60; Increase to >100;<br>n=3,3,4    | 0 | 0 | 0 |  |
| HR; Week 64; Decrease to <60;<br>n=3,3,3     | 1 | 0 | 0 |  |
| HR; Week 64; Increase to >100;<br>n=3,3,3    | 0 | 0 | 0 |  |
| HR; Week 68; Decrease to <60;<br>n=4,2,2     | 1 | 0 | 2 |  |
| HR; Week 68; Increase to >100;<br>n=4,2,2    | 0 | 0 | 0 |  |
| HR; Week 72; Decrease to <60;<br>n=3,2,2     | 0 | 0 | 0 |  |
| HR; Week 72; Increase to >100;<br>n=3,2,2    | 0 | 0 | 0 |  |
| HR; Week 76; Decrease to <60;<br>n=4,1,2     | 1 | 0 | 0 |  |

|  |   |       |       |  |
|--|---|-------|-------|--|
| HR; Week 76; Increase to >100;<br>n=4,1,2        | 0 | 0     | 1     |  |
| HR; Week 80; Decrease to <60;<br>n=3,1,2         | 1 | 0     | 0     |  |
| HR; Week 80; Increase to >100;<br>n=3,1,2        | 0 | 0     | 0     |  |
| HR; Week 84; Decrease to <60;<br>n=3,1,1         | 0 | 0     | 0     |  |
| HR; Week 84; Increase to >100;<br>n=3,1,1        | 0 | 0     | 0     |  |
| HR; Week 88; Decrease to <60;<br>n=3,1,1         | 1 | 0     | 0     |  |
| HR; Week 88; Increase to >100;<br>n=3,1,1        | 0 | 0     | 0     |  |
| HR; Week 92; Decrease to <60;<br>n=3,1,1         | 1 | 0     | 0     |  |
| HR; Week 92; Increase to >100;<br>n=3,1,1        | 0 | 0     | 0     |  |
| HR; Week 96; Decrease to <60;<br>n=3,1,1         | 1 | 0     | 0     |  |
| HR; Week 96; Increase to >100;<br>n=3,1,1        | 0 | 0     | 0     |  |
| HR; Week 100; Decrease to <60;<br>n=3,1,1        | 0 | 0     | 0     |  |
| HR; Week 100; Increase to >100;<br>n=3,1,1       | 0 | 0     | 0     |  |
| HR; Week 104; Decrease to <60;<br>n=3,1,1        | 0 | 0     | 0     |  |
| HR; Week 104; Increase to >100;<br>n=3,1,1       | 0 | 0     | 0     |  |
| HR; Week 108; Decrease to <60;<br>n=2,0,1        | 1 | 99999 | 0     |  |
| HR; Week 108; Increase to >100;<br>n=2,0,1       | 0 | 99999 | 0     |  |
| HR; Week 112; Decrease to <60;<br>n=2,0,0        | 1 | 99999 | 99999 |  |
| HR; Week 112; Increase to >100; n=2,<br>0,0      | 0 | 99999 | 99999 |  |
| HR; Week 116; Decrease to <60; n=1,<br>0,0       | 0 | 99999 | 99999 |  |
| HR; Week 116; Increase to >100; n=1,<br>0,0      | 0 | 99999 | 99999 |  |
| HR; Week 120; Decrease to <60; n=1,<br>0,0       | 0 | 99999 | 99999 |  |
| HR; Week 120; Increase to >100; n=1,<br>0,0      | 0 | 99999 | 99999 |  |
| HR; Week 124; Decrease to <60; n=1,<br>0,0       | 0 | 99999 | 99999 |  |
| HR; Week 124; Increase to >100; n=1,<br>0,0      | 0 | 99999 | 99999 |  |
| SBP; Week 4; Any grade increase;<br>n=15,16,16   | 1 | 8     | 4     |  |
| SBP; Week 8; Any grade increase;<br>n=16,16,14   | 3 | 5     | 4     |  |
| SBP; Week 12; Any grade increase;<br>n=16,16,13  | 3 | 5     | 2     |  |
| SBP; Week 16; Any grade increase;<br>n=14,16,13  | 4 | 3     | 2     |  |
| SBP; Week 20; Any grade increase;<br>n=11,15, 13 | 2 | 3     | 1     |  |
| SBP; Week 24; Any grade increase;<br>n=12, 14,13 | 2 | 3     | 2     |  |

|   |   |       |       |
|---|---|-------|-------|
| SBP; Week 28; Any grade increase;<br>n=8, 12,7    | 2 | 0     | 0     |
| SBP; Week 32; Any grade increase;<br>n=7,11, 8    | 2 | 3     | 2     |
| SBP; Week 36; Any grade increase;<br>n=5, 11, 8   | 3 | 3     | 1     |
| SBP; Week 40; Any grade increase;<br>n=6,11, 7    | 1 | 4     | 2     |
| SBP; Week 44; Any grade increase;<br>n=5, 5, 4    | 2 | 0     | 0     |
| SBP; Week 48; Any grade increase;<br>n=5,4, 4     | 1 | 1     | 0     |
| SBP; Week 52; Any grade increase;<br>n=4,3, 4     | 1 | 0     | 0     |
| SBP; Week 56; Any grade increase;<br>n=4, 3, 4    | 0 | 0     | 0     |
| SBP; Week 60; Any grade increase;<br>n=3, 2, 4    | 1 | 1     | 0     |
| SBP; Week 64; Any grade increase;<br>n=3, 3, 3    | 1 | 0     | 0     |
| SBP; Week 68; Any grade increase;<br>n=4,2, 2     | 2 | 0     | 0     |
| SBP; Week 72; Any grade increase;<br>n=3,2, 2     | 1 | 0     | 0     |
| SBP; Week 76; Any grade increase;<br>n=4, 1, 2    | 2 | 0     | 0     |
| SBP; Week 80; Any grade increase;<br>n=3, 1, 2    | 2 | 0     | 0     |
| SBP; Week 84; Any grade increase;<br>n=3, 1,1     | 2 | 0     | 0     |
| SBP; Week 88; Any grade increase;<br>n=3, 1,1     | 0 | 0     | 0     |
| SBP; Week 92; Any grade increase;<br>n=3, 1, 1    | 2 | 0     | 0     |
| SBP; Week 96; Any grade increase;<br>n=3,1, 1     | 2 | 1     | 0     |
| SBP; Week 100; Any grade increase;<br>n=3, 1, 1   | 0 | 0     | 0     |
| SBP; Week 104; Any grade increase;<br>n=3, 1, 1   | 1 | 0     | 0     |
| SBP; Week 108; Any grade increase;<br>n=2,0, 1    | 1 | 99999 | 0     |
| SBP; Week 112; Any grade increase;<br>n=2, 0, 0   | 0 | 99999 | 99999 |
| SBP; Week 116; Any grade increase;<br>n=1, 0, 0   | 0 | 99999 | 99999 |
| SBP; Week 120; Any grade increase;<br>n=1, 0, 0   | 0 | 99999 | 99999 |
| SBP; Week 124; Any grade increase;<br>n=1, 0, 0   | 0 | 99999 | 99999 |
| DBP; Week 4; Any grade increase;<br>n=15, 16, 16  | 2 | 10    | 5     |
| DBP; Week 8; Any grade increase;<br>n=16, 16,14   | 4 | 8     | 3     |
| DBP; Week 12; Any grade increase;<br>n=16, 16, 13 | 4 | 4     | 2     |
| DBP; Week 16; Any grade increase;<br>n=14, 16,13  | 5 | 5     | 3     |
| DBP; Week 20; Any grade increase;<br>n=11, 15,13  | 4 | 5     | 2     |
| DBP; Week 24; Any grade increase;<br>n=12, 14,13  | 3 | 3     | 1     |

|  |   |       |       |  |
|--|---|-------|-------|--|
| DBP; Week 28; Any grade increase;<br>n=8, 12,7 | 1 | 2     | 0     |  |
| DBP; Week 32; Any grade increase;<br>n=7, 11,8 | 2 | 3     | 1     |  |
| DBP; Week 36; Any grade increase;<br>n=5, 11,8 | 2 | 1     | 2     |  |
| DBP; Week 40; Any grade increase;<br>n=6, 11,7 | 1 | 1     | 1     |  |
| DBP; Week 44; Any grade increase;<br>n=5, 5,4  | 4 | 1     | 2     |  |
| DBP; Week 48; Any grade increase;<br>n=5, 4,4  | 2 | 1     | 2     |  |
| DBP; Week 52; Any grade increase;<br>n=4,3,4   | 2 | 0     | 0     |  |
| DBP; Week 56; Any grade increase;<br>n=4,3,4   | 1 | 1     | 0     |  |
| DBP; Week 60; Any grade increase;<br>n=3,2,4   | 2 | 0     | 0     |  |
| DBP; Week 64; Any grade increase;<br>n=3,3, 3  | 1 | 0     | 1     |  |
| DBP; Week 68; Any grade increase;<br>n=4,2, 2  | 2 | 0     | 1     |  |
| DBP; Week 72; Any grade increase;<br>n=3,2,2   | 1 | 0     | 1     |  |
| DBP; Week 76; Any grade increase;<br>n=4,1,2   | 2 | 0     | 1     |  |
| DBP; Week 80; Any grade increase;<br>n=3,1,2   | 1 | 0     | 1     |  |
| DBP; Week 84; Any grade increase;<br>n=3,1,1   | 1 | 0     | 0     |  |
| DBP; Week 88; Any grade increase;<br>n=3,1,1   | 1 | 0     | 0     |  |
| DBP; Week 92; Any grade increase;<br>n=3, 1,1  | 1 | 0     | 1     |  |
| DBP; Week 96; Any grade increase;<br>n=3, 1,1  | 2 | 0     | 1     |  |
| DBP; Week 100; Any grade increase;<br>n=3,1,1  | 1 | 0     | 0     |  |
| DBP; Week 104; Any grade increase;<br>n=3,1,1  | 1 | 0     | 1     |  |
| DBP; Week 108; Any grade increase;<br>n=2,0,1  | 1 | 99999 | 0     |  |
| DBP; Week 112; Any grade increase;<br>n=2,0,0  | 0 | 99999 | 99999 |  |
| DBP; Week 116; Any grade increase;<br>n=1,0,0  | 0 | 99999 | 99999 |  |
| DBP; Week 120; Any grade increase;<br>n=1,0,0  | 0 | 99999 | 99999 |  |
| DBP; Week 124; Any grade increase;<br>n=1,0,0  | 0 | 99999 | 99999 |  |

Notes:

[11] - Safety Population

[12] - Safety Population

[13] - Safety Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants undergoing physical examinations

|   |   |
|---|---|
| End point title   | Number of participants undergoing physical examinations |
| End point description:<br>Complete physical examination included assessments of eyes, neurological and cardiovascular systems, lungs, abdomen, and any other areas with signs and symptoms of disease, and of the head, neck, ears, nose, mouth, throat, thyroid, lymph nodes, extremities, and a full skin exam to assess cutaneous malignancies and proliferative skin diseases. The data was not collected for this analysis since the study was terminated early. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Up to 3.2 years   |   |

| <b>End point values</b>     | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|-----------------------------|--|--|---------------------|--|
| Subject group type          | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed | 0 <sup>[14]</sup>                          | 0 <sup>[15]</sup>                          | 0 <sup>[16]</sup>   |  |
| Units: Participants         |  |  |                     |  |
| Participants                |  |  |                     |  |

Notes:

[14] - Safety Population

[15] - Safety Population

[16] - Safety Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with change in eastern cooperative oncology group (ECOG) performance status scores from Baseline

|   |   |
|---|---|
| End point title   | Number of participants with change in eastern cooperative oncology group (ECOG) performance status scores from Baseline |
| End point description:<br>The ECOG scale of performance status describes the level of functioning of participants in terms of their ability to care for themselves, daily activity, and physical ability. The ECOG performance was recorded as per ECOG performance status grades ranging from 0 (fully active, able to carry on all pre-disease performance without restriction) to 5 (dead). Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus Baseline value. The Baseline performance status of participants with respect to worst-case on-therapy performance status has been presented. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline and up to 3.2 years  |   |

| <b>End point values</b>     | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|-----------------------------|--|--|---------------------|--|
| Subject group type          | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed | 16 <sup>[17]</sup>                         | 16 <sup>[18]</sup>                         | 16 <sup>[19]</sup>  |  |
| Units: Participants         |  |  |                     |  |
| 0 to 0                      | 5  | 5  | 6                   |  |
| 0 to 1                      | 0  | 0  | 1                   |  |
| 0 to 2                      | 0  | 0  | 0                   |  |
| 0 to 3                      | 0  | 0  | 0                   |  |
| 0 to 4-5                    | 0  | 0  | 0                   |  |
| 1 to 0                      | 6  | 10   | 5                   |  |
| 1 to 1                      | 3  | 1  | 2                   |  |
| 1 to 2                      | 0  | 0  | 0                   |  |
| 1 to 3                      | 0  | 0  | 0                   |  |
| 1 to 4-5                    | 0  | 0  | 0                   |  |
| 2 to 0                      | 0  | 0  | 0                   |  |
| 2 to 1                      | 2  | 0  | 2                   |  |
| 2 to 2                      | 0  | 0  | 0                   |  |
| 2 to 3                      | 0  | 0  | 0                   |  |
| 2 to 4-5                    | 0  | 0  | 0                   |  |
| 3 to 0                      | 0  | 0  | 0                   |  |
| 3 to 1                      | 0  | 0  | 0                   |  |
| 3 to 2                      | 0  | 0  | 0                   |  |
| 3 to 3                      | 0  | 0  | 0                   |  |
| 3 to 4-5                    | 0  | 0  | 0                   |  |
| 4-5 to 0                    | 0  | 0  | 0                   |  |
| 4-5 to 1                    | 0  | 0  | 0                   |  |
| 4-5 to 2                    | 0  | 0  | 0                   |  |
| 4-5 to 3                    | 0  | 0  | 0                   |  |
| 4-5 to 4-5                  | 0  | 0  | 0                   |  |

Notes:

[17] - Safety Population

[18] - Safety Population

[19] - Safety Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with abnormal electrocardiograms (ECG) findings

|                 |  |
|-----------------|--|
| End point title | Number of participants with abnormal electrocardiograms (ECG) findings |
|-----------------|--|

End point description:

Single measurements of 12-lead ECGs were obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, corrected QT interval (QTc), Bazett's Corrected QT interval (QTcB), Friderica's Corrected QT interval (QTcF). Number of participants with abnormal ECG findings (Abnormal - Not Clinically Significant and Abnormal - Clinically Significant ) at any time post-Baseline visit have been presented.

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

End point timeframe:

Up to 3.2 years

| <b>End point values</b>               | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|---------------------------------------|--|--|---------------------|--|
| Subject group type                    | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed           | 16 <sup>[20]</sup>                         | 16 <sup>[21]</sup>                         | 16 <sup>[22]</sup>  |  |
| Units: Participants                   |  |  |                     |  |
| Abnormal - Not Clinically Significant | 9  | 10   | 9                   |  |
| Abnormal - Clinically Significant     | 0  | 1  | 0                   |  |

Notes:

[20] - Safety Population

[21] - Safety Population

[22] - Safety Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with absolute change in left ventricular ejection fraction from Baseline

|                 |   |
|-----------------|---|
| End point title | Number of participants with absolute change in left ventricular ejection fraction from Baseline |
|-----------------|---|

End point description:

Echocardiograms (ECHO) was performed to assess cardiac ejection fraction and cardiac valve morphology. Baseline was defined as the most recent non-missing value prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus Baseline value. The worst-case on-therapy value has been presented. "99999" represents data is not available.

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

End point timeframe:

Baseline and up to 3.2 years

| <b>End point values</b>                         | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|---|--|--|---------------------|--|
| Subject group type                              | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed                     | 16 <sup>[23]</sup>                         | 16 <sup>[24]</sup>                         | 16 <sup>[25]</sup>  |  |
| Units: Participants                             |  |  |                     |  |
| No Change Or Any Increase                       | 11   | 14   | 11                  |  |
| >0-<10 Decrease                                 | 4  | 2  | 3                   |  |
| >=10 Decrease And >= Lower limit of Normal (Ln) | 1  | 99999                                      | 2                   |  |

Notes:

[23] - Safety Population

[24] - Safety Population

[25] - Safety Population

### Statistical analyses

**Secondary: Number of participants with change in clinical chemistry parameters from Baseline**

|  |   |
|--|---|
| End point title  | Number of participants with change in clinical chemistry parameters from Baseline |
| End point description:   |   |
| Blood samples were collected for evaluation of clinical chemistry parameters including sodium, potassium, calcium, albumin, total protein, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GCT), phosphate, C-reactive protein (CRP), hypercalcemia, hyperkalemia, hyponatremia, hypocalcemia, hypokalemia, hyponatremia, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin and estimated creatinine clearance (CRTCE). Baseline was defined as the most recent non-missing value from a central laboratory prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus Baseline value. The worst-case on therapy value for number of participants with any grade increase in clinical chemistry parameters for has been presented. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline and up to 3.2 years   |   |

| End point values                 | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|----------------------------------|--|--|---------------------|--|
| Subject group type               | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed      | 16 <sup>[26]</sup>                         | 16 <sup>[27]</sup>                         | 16 <sup>[28]</sup>  |  |
| Units: Participants              |  |  |                     |  |
| ALT; n=16,16,16                  | 3  | 13   | 9                   |  |
| Albumin; n=16,16,16              | 2  | 5  | 2                   |  |
| Alkaline phosphatase; n=16,16,16 | 5  | 10   | 4                   |  |
| AST; n=16,16,16                  | 8  | 15   | 12                  |  |
| Bilirubin; n=16,16,16            | 0  | 2  | 0                   |  |
| CRP; n=12,12,13                  | 0  | 0  | 0                   |  |
| Creatinine; n=16,16,16           | 0  | 0  | 0                   |  |
| Direct bilirubin; n=4,6,3        | 0  | 0  | 0                   |  |
| GCT; n=16,16,16                  | 6  | 12   | 5                   |  |
| Hypercalcemia; n=16,16,16        | 0  | 0  | 0                   |  |
| Hyperkalemia; n=16,16,16         | 1  | 4  | 0                   |  |
| Hyponatremia; n=16,16,16         | 3  | 4  | 1                   |  |
| Hypocalcemia; n=16,16,16         | 7  | 7  | 4                   |  |
| Hypokalemia; n=16,16,16          | 1  | 4  | 3                   |  |
| Hyponatremia; n=16,16,16         | 7  | 7  | 5                   |  |
| LDH; 16,16,15                    | 0  | 0  | 0                   |  |
| Phosphate; n=16,16,16            | 10   | 6  | 4                   |  |
| Protein; n=16,16,16              | 0  | 0  | 0                   |  |
| Urea; n=15,15,16                 | 0  | 0  | 0                   |  |
| CRTCE; n=5,2,5                   | 0  | 0  | 0                   |  |

Notes:

[26] - Safety Population

[27] - Safety Population

[28] - Safety Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with change in hematology parameters from Baseline

|                 |   |
|-----------------|---|
| End point title | Number of participants with change in hematology parameters from Baseline |
|-----------------|---|

End point description:

Blood samples were collected for evaluation of hematology parameters including hemoglobin, white blood cell (WBC), platelet count, basophils, eosinophils, lymphocytes, monocytes, total neutrophils, lymphocytopenia and lymphocytosis. Baseline was defined as the most recent non-missing value from a central laboratory prior to the first dose of study treatment. Change from Baseline was defined as any visit value minus Baseline value. The worst-case on therapy value for number of participants with any grade increase in hematology parameters for has been presented.

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

End point timeframe:

Baseline and up to 3.2 years

| End point values            | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|-----------------------------|--|--|---------------------|--|
| Subject group type          | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed | 16 <sup>[29]</sup>                         | 16 <sup>[30]</sup>                         | 16 <sup>[31]</sup>  |  |
| Units: Participants         |  |  |                     |  |
| Basophils                   | 0  | 0  | 0                   |  |
| Eosinophils                 | 0  | 0  | 0                   |  |
| Hemoglobin                  | 4  | 6  | 4                   |  |
| Leukocytes                  | 5  | 9  | 10                  |  |
| Monocytes                   | 0  | 0  | 0                   |  |
| Neutrophils                 | 6  | 9  | 9                   |  |
| Platelets                   | 2  | 5  | 3                   |  |
| Lymphocytopenia             | 8  | 6  | 6                   |  |
| Lymphocytosis               | 2  | 0  | 0                   |  |

Notes:

[29] - Safety Population

[30] - Safety Population

[31] - Safety Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with incidence of squamous cell carcinoma and keratoacanthoma

|                 |  |
|-----------------|--|
| End point title | Number of participants with incidence of squamous cell carcinoma and keratoacanthoma |
|-----------------|--|

End point description:

The safety profile of dabrafenib and trametinib in monotherapy as well as in combination therapy was characterized by determining the number of participants with incidence of squamous cell carcinoma and keratoacanthoma.

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

End point timeframe:

Up to 3.2 years

| <b>End point values</b>     | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|-----------------------------|--|--|---------------------|--|
| Subject group type          | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed | 16 <sup>[32]</sup>                         | 16 <sup>[33]</sup>                         | 16 <sup>[34]</sup>  |  |
| Units: Participants         |  |  |                     |  |
| Participants                | 1  | 0  | 0                   |  |

Notes:

[32] - Safety Population

[33] - Safety Population

[34] - Safety Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with adverse events (AEs) and serious AEs

|                 |  |
|-----------------|--|
| End point title | Number of participants with adverse events (AEs) and serious AEs |
|-----------------|--|

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. SAE is defined as any untoward medical occurrence that, at any dose results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability, is a congenital anomaly/ birth effect, other situations and is associated with liver injury or impaired liver function.

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

End point timeframe:

Up to 3.2 years

| <b>End point values</b>     | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|-----------------------------|--|--|---------------------|--|
| Subject group type          | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed | 16 <sup>[35]</sup>                         | 16 <sup>[36]</sup>                         | 16 <sup>[37]</sup>  |  |
| Units: Participants         |  |  |                     |  |
| Any AE                      | 16   | 16   | 15                  |  |
| Any SAE                     | 8  | 7  | 4                   |  |

Notes:

[35] - Safety Population

[36] - Safety Population

[37] - Safety Population

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Plasma pharmacokinetic concentration of trametinib and dabrafenib**

---

|                 |   |
|-----------------|---|
| End point title | Plasma pharmacokinetic concentration of trametinib and dabrafenib |
|-----------------|---|

End point description:

This analysis was planned but not performed since the study was terminated early due to slow enrollment and limited numbers of viable tissue samples. Hence, data for this analysis has not been presented.

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

End point timeframe:

Pre-dose and Post-dose up to Week 10

---

| <b>End point values</b>                 | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |  |
|---|--|--|---------------------|--|
| Subject group type                      | Reporting group                            | Reporting group                            | Reporting group     |  |
| Number of subjects analysed             | 0 <sup>[38]</sup>                          | 0 <sup>[39]</sup>                          | 0 <sup>[40]</sup>   |  |
| Units: Nanograms per milliliter (ng/mL) |  |  |                     |  |
| arithmetic mean (standard deviation)    |  |  |                     |  |
| Nanograms per milliliter (ng/mL)        | ()   | ()   | ()                  |  |

Notes:

[38] - Biomarker Population

[39] - Biomarker Population

[40] - Biomarker Population

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**Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of the study treatment until the Follow up (up to 3.2 years).

Adverse event reporting additional description:

AEs and SAEs were collected in Safety Population which included all the participants who received at least one dose of randomized treatment and was based on the actual treatment received.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Dabrafenib followed by combination therapy |
|-----------------------|--|

Reporting group description:

Eligible participants received dabrafenib 150 milligrams (mg) twice a day (BID) continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.

|                       |  |
|-----------------------|--|
| Reporting group title | Trametinib followed by combination therapy |
|-----------------------|--|

Reporting group description:

Eligible participants received trametinib 2 mg per day continuously during 8 weeks of monotherapy treatment followed by the combination of trametinib 2 mg once daily with dabrafenib 150 mg BID until disease progression, death or unacceptable toxicity.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Combination therapy |
|-----------------------|---------------------|

Reporting group description:

Eligible participants received trametinib 2 mg per day plus dabrafenib 150 mg BID continuously until disease progression, death or unacceptable toxicity.

| <b>Serious adverse events</b>                                       | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |
|---|--|--|---------------------|
| Total subjects affected by serious adverse events                   |  |  |                     |
| subjects affected / exposed   | 8 / 16 (50.00%)                            | 7 / 16 (43.75%)                            | 4 / 16 (25.00%)     |
| number of deaths (all causes)                                       | 1  | 0  | 2                   |
| number of deaths resulting from adverse events                      |  |  |                     |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |                     |
| Adenocarcinoma gastric  |  |  |                     |
| subjects affected / exposed   | 0 / 16 (0.00%)                             | 1 / 16 (6.25%)                             | 0 / 16 (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                          | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Lung adenocarcinoma stage 0                          |                 |                 |                |
| subjects affected / exposed                          | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (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          |
| Metastases to meninges                               |                 |                 |                |
| subjects affected / exposed                          | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (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          |
| Squamous cell carcinoma                              |                 |                 |                |
| subjects affected / exposed                          | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (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          |
| Vascular disorders                                   |                 |                 |                |
| Hypotension  |                 |                 |                |
| subjects affected / exposed                          | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (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          |
| Peripheral ischaemia                                 |                 |                 |                |
| subjects affected / exposed                          | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                 |                 |                |
| Pyrexia  |                 |                 |                |
| subjects affected / exposed                          | 2 / 16 (12.50%) | 3 / 16 (18.75%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all      | 2 / 3           | 4 / 4           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Reproductive system and breast disorders             |                 |                 |                |
| Metrorrhagia   |                 |                 |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                            | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (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          |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |                |                |
| Pneumothorax   |                |                |                |
| subjects affected / exposed                            | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |
| Pulmonary sarcoidosis                                  |                |                |                |
| subjects affected / exposed                            | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |
| <b>Psychiatric disorders</b>                           |                |                |                |
| Panic attack   |                |                |                |
| subjects affected / exposed                            | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (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          |
| <b>Cardiac disorders</b>                               |                |                |                |
| Left ventricular dysfunction                           |                |                |                |
| subjects affected / exposed                            | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |
| <b>Nervous system disorders</b>                        |                |                |                |
| Haemorrhage intracranial                               |                |                |                |
| subjects affected / exposed                            | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Peripheral sensory neuropathy                          |                |                |                |
| subjects affected / exposed                            | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (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          |
| Spinal cord compression                                |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (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          |
| <b>Blood and lymphatic system disorders</b>     |                |                |                |
| Histiocytosis haematophagic                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Neutropenia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |
| <b>Gastrointestinal disorders</b>               |                |                |                |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 3 / 3          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (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                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |
| Subileus  |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (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          |
| <b>Hepatobiliary disorders</b>                  |                |                |                |
| Hepatocellular injury                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Endocrine disorders                             |                |                |                |
| Adrenal insufficiency                           |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (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          |
| Infections and infestations                     |                |                |                |
| Cellulitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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          |

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

| <b>Non-serious adverse events</b>                                   | Dabrafenib followed by combination therapy | Trametinib followed by combination therapy | Combination therapy |
|---|--|--|---------------------|
| Total subjects affected by non-serious adverse events               |  |  |                     |
| subjects affected / exposed   | 16 / 16 (100.00%)                          | 16 / 16 (100.00%)                          | 15 / 16 (93.75%)    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |                     |
| Skin Papilloma  |  |  |                     |
| subjects affected / exposed   | 5 / 16 (31.25%)                            | 0 / 16 (0.00%)                             | 0 / 16 (0.00%)      |
| occurrences (all)   | 6  | 0  | 0                   |
| Papilloma   |  |  |                     |
| subjects affected / exposed   | 3 / 16 (18.75%)                            | 0 / 16 (0.00%)                             | 0 / 16 (0.00%)      |
| occurrences (all)   | 3  | 0  | 0                   |
| Basal Cell Carcinoma  |  |  |                     |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                              | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 2 / 16 (12.50%)<br>3 |
| Malignant Melanoma<br>subjects affected / exposed<br>occurrences (all)        | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| Metastases To Meninges<br>subjects affected / exposed<br>occurrences (all)    | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| Tumour Pain<br>subjects affected / exposed<br>occurrences (all)               | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| Haemangioma<br>subjects affected / exposed<br>occurrences (all)               | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  |
| Vascular disorders  |                      |                      |                      |
| Hot Flush<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 16 (6.25%)<br>3  | 0 / 16 (0.00%)<br>0  | 2 / 16 (12.50%)<br>2 |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)              | 1 / 16 (6.25%)<br>3  | 2 / 16 (12.50%)<br>3 | 1 / 16 (6.25%)<br>1  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)               | 3 / 16 (18.75%)<br>3 | 1 / 16 (6.25%)<br>1  | 1 / 16 (6.25%)<br>1  |
| Haematoma<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  |
| Lymphoedema<br>subjects affected / exposed<br>occurrences (all)               | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  |
| Peripheral Venous Disease<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  |
| General disorders and administration<br>site conditions                       |                      |                      |                      |

|                                    |                  |                  |                 |
|------------------------------------|------------------|------------------|-----------------|
| Pyrexia                            |                  |                  |                 |
| subjects affected / exposed        | 5 / 16 (31.25%)  | 13 / 16 (81.25%) | 6 / 16 (37.50%) |
| occurrences (all)                  | 12               | 49               | 18              |
| Hyperthermia                       |                  |                  |                 |
| subjects affected / exposed        | 4 / 16 (25.00%)  | 4 / 16 (25.00%)  | 4 / 16 (25.00%) |
| occurrences (all)                  | 13               | 15               | 22              |
| Asthenia                           |                  |                  |                 |
| subjects affected / exposed        | 10 / 16 (62.50%) | 10 / 16 (62.50%) | 9 / 16 (56.25%) |
| occurrences (all)                  | 14               | 20               | 17              |
| Chills                             |                  |                  |                 |
| subjects affected / exposed        | 3 / 16 (18.75%)  | 10 / 16 (62.50%) | 4 / 16 (25.00%) |
| occurrences (all)                  | 4                | 15               | 8               |
| Oedema Peripheral                  |                  |                  |                 |
| subjects affected / exposed        | 4 / 16 (25.00%)  | 6 / 16 (37.50%)  | 4 / 16 (25.00%) |
| occurrences (all)                  | 7                | 8                | 4               |
| Chest Pain                         |                  |                  |                 |
| subjects affected / exposed        | 3 / 16 (18.75%)  | 1 / 16 (6.25%)   | 0 / 16 (0.00%)  |
| occurrences (all)                  | 6                | 2                | 0               |
| Mucosal Inflammation               |                  |                  |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)   | 4 / 16 (25.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                  | 1                | 4                | 1               |
| Influenza Like Illness             |                  |                  |                 |
| subjects affected / exposed        | 3 / 16 (18.75%)  | 2 / 16 (12.50%)  | 3 / 16 (18.75%) |
| occurrences (all)                  | 3                | 2                | 3               |
| Xerosis                            |                  |                  |                 |
| subjects affected / exposed        | 3 / 16 (18.75%)  | 2 / 16 (12.50%)  | 0 / 16 (0.00%)  |
| occurrences (all)                  | 3                | 2                | 0               |
| Malaise                            |                  |                  |                 |
| subjects affected / exposed        | 0 / 16 (0.00%)   | 0 / 16 (0.00%)   | 2 / 16 (12.50%) |
| occurrences (all)                  | 0                | 0                | 2               |
| Chest Discomfort                   |                  |                  |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)   | 0 / 16 (0.00%)   | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1                | 0                | 0               |
| Feeling Of Body Temperature Change |                  |                  |                 |
| subjects affected / exposed        | 1 / 16 (6.25%)   | 0 / 16 (0.00%)   | 0 / 16 (0.00%)  |
| occurrences (all)                  | 1                | 0                | 0               |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Ill-Defined Disorder                     |                |                |                |
| subjects affected / exposed              | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0              |
| Discomfort                               |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0              |
| Face Oedema                              |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0              |
| Inflammation                             |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0              |
| Inflammatory Pain                        |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0              |
| Mucosal Dryness                          |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0              |
| Nodule                                   |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                        | 0              | 1              | 0              |
| Hernia                                   |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                        | 0              | 0              | 1              |
| Hypothermia                              |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                        | 0              | 0              | 1              |
| Oedema Due To Cardiac Disease            |                |                |                |
| subjects affected / exposed              | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                        | 0              | 0              | 1              |
| Immune system disorders                  |                |                |                |
| Allergy To Arthropod Sting               |                |                |                |
| subjects affected / exposed              | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)                        | 1              | 0              | 0              |
| Reproductive system and breast disorders |                |                |                |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Amenorrhoea                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1               | 1               | 0               |
| Erectile Dysfunction                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Vulvovaginal Dryness                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Breast Pain                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Vaginal Haemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Vulvovaginal Pruritus                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Adenomyosis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Cough   |                 |                 |                 |
| subjects affected / exposed                     | 4 / 16 (25.00%) | 3 / 16 (18.75%) | 2 / 16 (12.50%) |
| occurrences (all)                               | 6               | 4               | 2               |
| Epistaxis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 4 / 16 (25.00%) | 2 / 16 (12.50%) |
| occurrences (all)                               | 0               | 5               | 4               |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 16 (18.75%) | 3 / 16 (18.75%) | 0 / 16 (0.00%)  |
| occurrences (all)                               | 3               | 3               | 0               |
| Nasal Dryness                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 2 / 16 (12.50%) | 1 / 16 (6.25%)  |
| occurrences (all)                               | 1               | 3               | 1               |
| Rhinitis Allergic                               |                 |                 |                 |

|                                    |                |                 |                |
|------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed        | 0 / 16 (0.00%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all)                  | 0              | 3               | 0              |
| Dry Throat                         |                |                 |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all)                  | 1              | 2               | 0              |
| Dyspnoea Exertional                |                |                 |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all)                  | 1              | 2               | 0              |
| Oropharyngeal Pain                 |                |                 |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all)                  | 1              | 2               | 0              |
| Pneumonitis                        |                |                 |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 0              | 2               | 0              |
| Rhinorrhoea                        |                |                 |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all)                  | 0              | 2               | 0              |
| Asthma                             |                |                 |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0              |
| Catarrh                            |                |                 |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 1 / 16 (6.25%)  | 1 / 16 (6.25%) |
| occurrences (all)                  | 1              | 1               | 1              |
| Lower Respiratory Tract Congestion |                |                 |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0              |
| Productive Cough                   |                |                 |                |
| subjects affected / exposed        | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0              |
| Atelectasis                        |                |                 |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 0              | 1               | 0              |
| Oropharyngeal Discomfort           |                |                 |                |
| subjects affected / exposed        | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)                  | 0              | 1               | 0              |
| Dysphonia                          |                |                 |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Psychiatric disorders                            |                     |                     |                     |
| Insomnia   |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 1 / 16 (6.25%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                | 2                   | 1                   | 0                   |
| Anxiety  |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 2 / 16 (12.50%)     | 0 / 16 (0.00%)      |
| occurrences (all)                                | 1                   | 2                   | 0                   |
| Irritability                                     |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 16 (0.00%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Mood Altered                                     |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 16 (0.00%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Sleep Disorder                                   |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 1 / 16 (6.25%)      | 1 / 16 (6.25%)      |
| occurrences (all)                                | 1                   | 1                   | 1                   |
| Stress   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 16 (6.25%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Depression                                       |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 16 (6.25%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Hallucination                                    |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 16 (6.25%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Investigations                                   |                     |                     |                     |
| Alanine Aminotransferase Increased               |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 5 / 16 (31.25%)     | 0 / 16 (0.00%)      |
| occurrences (all)                                | 0                   | 15                  | 0                   |
| Aspartate Aminotransferase Increased             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 5 / 16 (31.25%)     | 0 / 16 (0.00%)      |
| occurrences (all)                                | 0                   | 14                  | 0                   |
| Gamma-Glutamyltransferase Increased              |                     |                     |                     |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed            | 1 / 16 (6.25%)  | 2 / 16 (12.50%) | 1 / 16 (6.25%)  |
| occurrences (all)                      | 1               | 10              | 1               |
| Blood Creatine Phosphokinase Increased |                 |                 |                 |
| subjects affected / exposed            | 5 / 16 (31.25%) | 7 / 16 (43.75%) | 5 / 16 (31.25%) |
| occurrences (all)                      | 8               | 9               | 7               |
| Blood Alkaline Phosphatase Increased   |                 |                 |                 |
| subjects affected / exposed            | 1 / 16 (6.25%)  | 2 / 16 (12.50%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 1               | 7               | 0               |
| Lipase Increased                       |                 |                 |                 |
| subjects affected / exposed            | 1 / 16 (6.25%)  | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences (all)                      | 2               | 4               | 2               |
| Blood Lactate Dehydrogenase Increased  |                 |                 |                 |
| subjects affected / exposed            | 1 / 16 (6.25%)  | 2 / 16 (12.50%) | 1 / 16 (6.25%)  |
| occurrences (all)                      | 1               | 3               | 1               |
| C-Reactive Protein Increased           |                 |                 |                 |
| subjects affected / exposed            | 1 / 16 (6.25%)  | 3 / 16 (18.75%) | 0 / 16 (0.00%)  |
| occurrences (all)                      | 1               | 3               | 0               |
| Ejection Fraction Decreased            |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 3 / 16 (18.75%) | 1 / 16 (6.25%)  |
| occurrences (all)                      | 0               | 3               | 1               |
| Electrocardiogram Qt Prolonged         |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                      | 0               | 3               | 0               |
| Weight Decreased                       |                 |                 |                 |
| subjects affected / exposed            | 2 / 16 (12.50%) | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  |
| occurrences (all)                      | 2               | 2               | 1               |
| Amylase Increased                      |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  |
| occurrences (all)                      | 0               | 2               | 1               |
| Blood Triglycerides Increased          |                 |                 |                 |
| subjects affected / exposed            | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                      | 0               | 0               | 2               |
| Neutrophil Count Decreased             |                 |                 |                 |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 1 / 16 (6.25%)<br>2 |
| Intraocular Pressure Increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| White Blood Cell Count Increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Blood Albumin Decreased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Platelet Count Decreased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Weight Increased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 |
| Blood Fibrinogen Increased<br>subjects affected / exposed<br>occurrences (all)       | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Hepatic Enzyme Increased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| Injury, poisoning and procedural complications                                       |                     |                     |                     |
| Foot Fracture<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 16 (6.25%)<br>2 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Arthropod Bite<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Ligament Sprain<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 |
| Limb Injury  |                     |                     |                     |

|                              |                |                |                |
|------------------------------|----------------|----------------|----------------|
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Procedural Pain              |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Traumatic Haematoma          |                |                |                |
| subjects affected / exposed  | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Fall                         |                |                |                |
| subjects affected / exposed  | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)            | 0              | 0              | 1              |
| Cardiac disorders            |                |                |                |
| Bradycardia                  |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 1              | 0              |
| Palpitations                 |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 1              | 0              |
| Sinus Bradycardia            |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Tachycardia                  |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)            | 1              | 0              | 1              |
| Extrasystoles                |                |                |                |
| subjects affected / exposed  | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Tricuspid Valve Incompetence |                |                |                |
| subjects affected / exposed  | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)            | 0              | 1              | 0              |
| Atrial Fibrillation          |                |                |                |
| subjects affected / exposed  | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)            | 0              | 0              | 1              |
| Mitral Valve Incompetence    |                |                |                |
| subjects affected / exposed  | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)            | 0              | 0              | 1              |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Nervous system disorders    |                 |                 |                 |
| Headache                    |                 |                 |                 |
| subjects affected / exposed | 9 / 16 (56.25%) | 9 / 16 (56.25%) | 6 / 16 (37.50%) |
| occurrences (all)           | 16              | 15              | 9               |
| Tremor                      |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 3 / 16 (18.75%) |
| occurrences (all)           | 0               | 1               | 7               |
| Paraesthesia                |                 |                 |                 |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 5               | 0               | 1               |
| Dizziness                   |                 |                 |                 |
| subjects affected / exposed | 3 / 16 (18.75%) | 1 / 16 (6.25%)  | 2 / 16 (12.50%) |
| occurrences (all)           | 3               | 1               | 2               |
| Hyperaesthesia              |                 |                 |                 |
| subjects affected / exposed | 3 / 16 (18.75%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 3               | 1               | 0               |
| Burning Sensation           |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Dysaesthesia                |                 |                 |                 |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 2               | 0               | 2               |
| Cervical Radiculopathy      |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Epilepsy                    |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Neuralgia                   |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 1               | 0               | 1               |
| Sciatica                    |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Syncope                     |                 |                 |                 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                 | 1 / 16 (6.25%) | 1 / 16 (6.25%) | 1 / 16 (6.25%) |
| occurrences (all)                           | 1              | 1              | 1              |
| <b>Amnesia</b>                              |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| <b>Aphasia</b>                              |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| <b>Memory Impairment</b>                    |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| <b>Migraine With Aura</b>                   |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| <b>Presyncope</b>                           |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| <b>Stupor</b>                               |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)                           | 0              | 1              | 0              |
| <b>Demyelinating Polyneuropathy</b>         |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                           | 0              | 0              | 1              |
| <b>Head Discomfort</b>                      |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                           | 0              | 0              | 1              |
| <b>Hypoaesthesia</b>                        |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                           | 0              | 0              | 1              |
| <b>Muscle Contractions Involuntary</b>      |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                           | 0              | 0              | 1              |
| <b>Peripheral Sensory Neuropathy</b>        |                |                |                |
| subjects affected / exposed                 | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)                           | 0              | 0              | 1              |
| <b>Blood and lymphatic system disorders</b> |                |                |                |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Neutropenia                 |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 3 / 16 (18.75%) | 3 / 16 (18.75%) |
| occurrences (all)           | 1               | 14              | 4               |
| Anaemia                     |                 |                 |                 |
| subjects affected / exposed | 4 / 16 (25.00%) | 1 / 16 (6.25%)  | 2 / 16 (12.50%) |
| occurrences (all)           | 4               | 1               | 3               |
| Eosinophilia                |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Leukopenia                  |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Lymphadenitis               |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0               | 1               | 1               |
| Thrombocytopenia            |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0               | 1               | 1               |
| Histiocytosis Haematophagic |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Ear and labyrinth disorders |                 |                 |                 |
| Vertigo                     |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Eye disorders               |                 |                 |                 |
| Visual Impairment           |                 |                 |                 |
| subjects affected / exposed | 2 / 16 (12.50%) | 1 / 16 (6.25%)  | 2 / 16 (12.50%) |
| occurrences (all)           | 3               | 2               | 2               |
| Eye Pain                    |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 2 / 16 (12.50%) | 1 / 16 (6.25%)  |
| occurrences (all)           | 0               | 3               | 1               |
| Dry Eye                     |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 2 / 16 (12.50%) | 1 / 16 (6.25%)  |
| occurrences (all)           | 1               | 2               | 1               |
| Iridocyclitis               |                 |                 |                 |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 2               | 0              |
| Vision Blurred              |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 16 (12.50%) | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 2               | 0              |
| Eyelid Ptosis               |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Keratitis                   |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Ocular Hyperaemia           |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Visual Acuity Reduced       |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 1 / 16 (6.25%)  | 1 / 16 (6.25%) |
| occurrences (all)           | 1              | 1               | 1              |
| Eyelid Oedema               |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Uveitis                     |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Chalazion                   |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 0               | 1              |
| Chorioretinopathy           |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 0               | 1              |
| Conjunctival Hyperaemia     |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 0               | 1              |
| Diplopia                    |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 0               | 1              |
| Vitreous Detachment         |                |                 |                |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| <b>Gastrointestinal disorders</b>                |                     |                     |                     |
| <b>Diarrhoea</b>                                 |                     |                     |                     |
| subjects affected / exposed                      | 6 / 16 (37.50%)     | 7 / 16 (43.75%)     | 5 / 16 (31.25%)     |
| occurrences (all)                                | 9                   | 19                  | 7                   |
| <b>Nausea</b>                                    |                     |                     |                     |
| subjects affected / exposed                      | 8 / 16 (50.00%)     | 4 / 16 (25.00%)     | 5 / 16 (31.25%)     |
| occurrences (all)                                | 12                  | 11                  | 5                   |
| <b>Vomiting</b>                                  |                     |                     |                     |
| subjects affected / exposed                      | 4 / 16 (25.00%)     | 4 / 16 (25.00%)     | 3 / 16 (18.75%)     |
| occurrences (all)                                | 6                   | 9                   | 3                   |
| <b>Constipation</b>                              |                     |                     |                     |
| subjects affected / exposed                      | 2 / 16 (12.50%)     | 5 / 16 (31.25%)     | 2 / 16 (12.50%)     |
| occurrences (all)                                | 6                   | 6                   | 3                   |
| <b>Abdominal Pain</b>                            |                     |                     |                     |
| subjects affected / exposed                      | 2 / 16 (12.50%)     | 2 / 16 (12.50%)     | 1 / 16 (6.25%)      |
| occurrences (all)                                | 4                   | 6                   | 1                   |
| <b>Abdominal Pain Upper</b>                      |                     |                     |                     |
| subjects affected / exposed                      | 4 / 16 (25.00%)     | 4 / 16 (25.00%)     | 0 / 16 (0.00%)      |
| occurrences (all)                                | 4                   | 5                   | 0                   |
| <b>Abdominal Distension</b>                      |                     |                     |                     |
| subjects affected / exposed                      | 2 / 16 (12.50%)     | 0 / 16 (0.00%)      | 1 / 16 (6.25%)      |
| occurrences (all)                                | 4                   | 0                   | 1                   |
| <b>Dry Mouth</b>                                 |                     |                     |                     |
| subjects affected / exposed                      | 2 / 16 (12.50%)     | 4 / 16 (25.00%)     | 3 / 16 (18.75%)     |
| occurrences (all)                                | 3                   | 4                   | 3                   |
| <b>Gastroesophageal Reflux Disease</b>           |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 2 / 16 (12.50%)     | 0 / 16 (0.00%)      |
| occurrences (all)                                | 1                   | 3                   | 0                   |
| <b>Dysphagia</b>                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 2 / 16 (12.50%)     | 0 / 16 (0.00%)      |
| occurrences (all)                                | 0                   | 2                   | 0                   |
| <b>Odynophagia</b>                               |                     |                     |                     |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 16 (0.00%)      | 1 / 16 (6.25%)      |
| occurrences (all)                                | 1                   | 0                   | 2                   |

|                              |                |                |                |
|------------------------------|----------------|----------------|----------------|
| Aerophagia                   |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Aphthous Ulcer               |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 1 / 16 (6.25%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 1              | 0              |
| Ascites                      |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Colitis                      |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Dyspepsia                    |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Gastrointestinal Disorder    |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Gastrointestinal Haemorrhage |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Gingival Pain                |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Mouth Ulceration             |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Painful Defaecation          |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |
| Rectal Haemorrhage           |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)            | 1              | 0              | 1              |
| Tooth Demineralisation       |                |                |                |
| subjects affected / exposed  | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all)            | 1              | 0              | 0              |

|  |                     |                      |                      |
|--|---------------------|----------------------|----------------------|
| Tooth Discolouration<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1 | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| Anal Fissure<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  |
| Food Poisoning<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  |
| Haematochezia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  |
| Salivary Hypersecretion<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  |
| Tongue Discolouration<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  |
| Cheilitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  |
| Gingival Bleeding<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  |
| Hepatobiliary disorders<br>Hepatocellular Injury<br>subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1 | 3 / 16 (18.75%)<br>3 | 2 / 16 (12.50%)<br>2 |
| Cholestasis<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 1 / 16 (6.25%)<br>1  |
| Hepatitis  |                     |                      |                      |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 |
| <b>Skin and subcutaneous tissue disorders</b>     |                     |                     |                     |
| <b>Rash</b>                                       |                     |                     |                     |
| subjects affected / exposed                       | 4 / 16 (25.00%)     | 8 / 16 (50.00%)     | 3 / 16 (18.75%)     |
| occurrences (all)                                 | 5                   | 15                  | 3                   |
| <b>Palmar-Plantar Erythrodysesthesia Syndrome</b> |                     |                     |                     |
| subjects affected / exposed                       | 6 / 16 (37.50%)     | 2 / 16 (12.50%)     | 1 / 16 (6.25%)      |
| occurrences (all)                                 | 9                   | 3                   | 1                   |
| <b>Palmoplantar Keratoderma</b>                   |                     |                     |                     |
| subjects affected / exposed                       | 7 / 16 (43.75%)     | 0 / 16 (0.00%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                 | 7                   | 0                   | 0                   |
| <b>Alopecia</b>                                   |                     |                     |                     |
| subjects affected / exposed                       | 4 / 16 (25.00%)     | 6 / 16 (37.50%)     | 1 / 16 (6.25%)      |
| occurrences (all)                                 | 6                   | 7                   | 1                   |
| <b>Dermatitis Acneiform</b>                       |                     |                     |                     |
| subjects affected / exposed                       | 0 / 16 (0.00%)      | 4 / 16 (25.00%)     | 1 / 16 (6.25%)      |
| occurrences (all)                                 | 0                   | 7                   | 1                   |
| <b>Night Sweats</b>                               |                     |                     |                     |
| subjects affected / exposed                       | 0 / 16 (0.00%)      | 3 / 16 (18.75%)     | 0 / 16 (0.00%)      |
| occurrences (all)                                 | 0                   | 5                   | 0                   |
| <b>Skin Lesion</b>                                |                     |                     |                     |
| subjects affected / exposed                       | 0 / 16 (0.00%)      | 0 / 16 (0.00%)      | 2 / 16 (12.50%)     |
| occurrences (all)                                 | 0                   | 0                   | 5                   |
| <b>Erythema Nodosum</b>                           |                     |                     |                     |
| subjects affected / exposed                       | 3 / 16 (18.75%)     | 1 / 16 (6.25%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                 | 4                   | 2                   | 0                   |
| <b>Hyperkeratosis</b>                             |                     |                     |                     |
| subjects affected / exposed                       | 3 / 16 (18.75%)     | 1 / 16 (6.25%)      | 2 / 16 (12.50%)     |
| occurrences (all)                                 | 4                   | 1                   | 2                   |
| <b>Keratosis Pilaris</b>                          |                     |                     |                     |
| subjects affected / exposed                       | 4 / 16 (25.00%)     | 0 / 16 (0.00%)      | 0 / 16 (0.00%)      |
| occurrences (all)                                 | 4                   | 0                   | 0                   |
| <b>Dry Skin</b>                                   |                     |                     |                     |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 3 / 16 (18.75%)<br>3 | 4 / 16 (25.00%)<br>4 | 3 / 16 (18.75%)<br>3 |
| <b>Pruritus</b>                                  |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 2 / 16 (12.50%)<br>2 | 3 / 16 (18.75%)<br>4 | 2 / 16 (12.50%)<br>3 |
| <b>Pigmentation Disorder</b>                     |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 3 / 16 (18.75%)<br>3 | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| <b>Panniculitis</b>                              |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 2 / 16 (12.50%)<br>3 | 0 / 16 (0.00%)<br>0  |
| <b>Erythema</b>                                  |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 2 / 16 (12.50%)<br>3 |
| <b>Onychoclasia</b>                              |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>2  | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| <b>Eczema</b>                                    |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 2 / 16 (12.50%)<br>2 | 1 / 16 (6.25%)<br>1  |
| <b>Rash Macular</b>                              |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 2 / 16 (12.50%)<br>2 | 1 / 16 (6.25%)<br>1  |
| <b>Skin Fissures</b>                             |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 2 / 16 (12.50%)<br>2 | 0 / 16 (0.00%)<br>0  |
| <b>Urticaria</b>                                 |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 1 / 16 (6.25%)<br>1  | 1 / 16 (6.25%)<br>2  |
| <b>Hyperhidrosis</b>                             |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  |
| <b>Intertrigo</b>                                |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| <b>Nail Dystrophy</b>                            |                      |                      |                      |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Nail Pigmentation           |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |
| Hypertrichosis              |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Nail Discolouration         |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Nail Disorder               |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Prurigo                     |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Rash Maculo-Papular         |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Seborrhoeic Dermatitis      |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Neutrophilic Panniculitis   |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 16 (0.00%)  | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 0               | 1              |
| Renal and urinary disorders |                |                 |                |
| Dysuria                     |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all)           | 1              | 2               | 1              |
| Haematuria                  |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 2               | 0              |
| Pollakiuria                 |                |                 |                |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 16 (0.00%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 1              | 0               | 0              |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Renal Failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Renal Tubular Acidosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Urinary Retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Endocrine disorders                             |                 |                 |                 |
| Adrenal Insufficiency                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Hyperthyroidism                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                               | 0               | 1               | 0               |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Back Pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 7 / 16 (43.75%) | 4 / 16 (25.00%) | 2 / 16 (12.50%) |
| occurrences (all)                               | 9               | 5               | 2               |
| Muscle Spasms                                   |                 |                 |                 |
| subjects affected / exposed                     | 5 / 16 (31.25%) | 6 / 16 (37.50%) | 2 / 16 (12.50%) |
| occurrences (all)                               | 7               | 9               | 2               |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 5 / 16 (31.25%) | 3 / 16 (18.75%) | 3 / 16 (18.75%) |
| occurrences (all)                               | 7               | 8               | 3               |
| Myalgia   |                 |                 |                 |
| subjects affected / exposed                     | 4 / 16 (25.00%) | 5 / 16 (31.25%) | 4 / 16 (25.00%) |
| occurrences (all)                               | 5               | 8               | 7               |
| Pain In Extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 3 / 16 (18.75%) | 5 / 16 (31.25%) | 3 / 16 (18.75%) |
| occurrences (all)                               | 7               | 7               | 5               |
| Neck Pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 2 / 16 (12.50%) | 2 / 16 (12.50%) |
| occurrences (all)                               | 1               | 6               | 3               |
| Musculoskeletal Stiffness                       |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 16 (18.75%) | 3 / 16 (18.75%) | 2 / 16 (12.50%) |
| occurrences (all)           | 3               | 5               | 2               |
| Groin Pain                  |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Musculoskeletal Pain        |                 |                 |                 |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 2               | 0               | 1               |
| Flank Pain                  |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0               | 0               | 2               |
| Limb Discomfort             |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 1               | 0               |
| Muscle Contracture          |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Muscular Weakness           |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 1               | 1               | 1               |
| Musculoskeletal Chest Pain  |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Osteoarthritis              |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Spinal Pain                 |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Tendonitis                  |                 |                 |                 |
| subjects affected / exposed | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Joint Stiffness             |                 |                 |                 |
| subjects affected / exposed | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Myopathy                    |                 |                 |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  |
| <b>Infections and infestations</b>               |                      |                      |                      |
| <b>Folliculitis</b>                              |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 7 / 16 (43.75%)<br>8 | 2 / 16 (12.50%)<br>2 |
| <b>Nasopharyngitis</b>                           |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 5 / 16 (31.25%)<br>5 | 3 / 16 (18.75%)<br>3 |
| <b>Urinary Tract Infection</b>                   |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 4 / 16 (25.00%)<br>4 | 3 / 16 (18.75%)<br>4 |
| <b>Bronchitis</b>                                |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 2 / 16 (12.50%)<br>3 | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  |
| <b>Gastroenteritis</b>                           |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 2 / 16 (12.50%)<br>2 | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  |
| <b>Influenza</b>                                 |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 2 / 16 (12.50%)<br>2 | 0 / 16 (0.00%)<br>0  | 0 / 16 (0.00%)<br>0  |
| <b>Cellulitis</b>                                |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>2  | 0 / 16 (0.00%)<br>0  |
| <b>Conjunctivitis</b>                            |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 2 / 16 (12.50%)<br>2 | 0 / 16 (0.00%)<br>0  |
| <b>Cystitis</b>                                  |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 1 / 16 (6.25%)<br>2  | 0 / 16 (0.00%)<br>0  |
| <b>Pharyngitis</b>                               |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 2 / 16 (12.50%)<br>2 | 1 / 16 (6.25%)<br>1  |
| <b>Rash Pustular</b>                             |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 16 (6.25%)<br>1  | 2 / 16 (12.50%)<br>2 | 0 / 16 (0.00%)<br>0  |

|                                       |                |                |                 |
|---------------------------------------|----------------|----------------|-----------------|
| Fungal Skin Infection                 |                |                |                 |
| subjects affected / exposed           | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all)                     | 0              | 0              | 2               |
| Paronychia                            |                |                |                 |
| subjects affected / exposed           | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%)  |
| occurrences (all)                     | 0              | 0              | 2               |
| Rhinitis                              |                |                |                 |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 2 / 16 (12.50%) |
| occurrences (all)                     | 0              | 1              | 2               |
| Erysipelas                            |                |                |                 |
| subjects affected / exposed           | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0               |
| Molluscum Contagiosum                 |                |                |                 |
| subjects affected / exposed           | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0               |
| Respiratory Syncytial Virus Infection |                |                |                 |
| subjects affected / exposed           | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0               |
| Streptococcal Sepsis                  |                |                |                 |
| subjects affected / exposed           | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0               |
| Tonsillitis                           |                |                |                 |
| subjects affected / exposed           | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0               |
| Tracheitis                            |                |                |                 |
| subjects affected / exposed           | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0               |
| Vulvovaginal Candidiasis              |                |                |                 |
| subjects affected / exposed           | 1 / 16 (6.25%) | 0 / 16 (0.00%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 1              | 0              | 0               |
| Vulvovaginal Mycotic Infection        |                |                |                 |
| subjects affected / exposed           | 1 / 16 (6.25%) | 1 / 16 (6.25%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 1              | 1              | 0               |
| Fungal Oesophagitis                   |                |                |                 |
| subjects affected / exposed           | 0 / 16 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (0.00%)  |
| occurrences (all)                     | 0              | 1              | 0               |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Lung Infection                          |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 0               | 1               | 0               |
| Moraxella Infection                     |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 0               | 1               | 0               |
| Sinusitis                               |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 0               | 1               | 0               |
| Escherichia Urinary Tract Infection     |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                       | 0               | 0               | 1               |
| Febrile Infection                       |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                       | 0               | 0               | 1               |
| Viral Rhinitis                          |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                       | 0               | 0               | 1               |
| Viral Upper Respiratory Tract Infection |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  | 1 / 16 (6.25%)  |
| occurrences (all)                       | 0               | 0               | 1               |
| Metabolism and nutrition disorders      |                 |                 |                 |
| Decreased Appetite                      |                 |                 |                 |
| subjects affected / exposed             | 1 / 16 (6.25%)  | 4 / 16 (25.00%) | 2 / 16 (12.50%) |
| occurrences (all)                       | 1               | 7               | 3               |
| Hypocalcaemia                           |                 |                 |                 |
| subjects affected / exposed             | 3 / 16 (18.75%) | 3 / 16 (18.75%) | 1 / 16 (6.25%)  |
| occurrences (all)                       | 4               | 3               | 1               |
| Hyperkalaemia                           |                 |                 |                 |
| subjects affected / exposed             | 0 / 16 (0.00%)  | 2 / 16 (12.50%) | 0 / 16 (0.00%)  |
| occurrences (all)                       | 0               | 3               | 0               |
| Increased Appetite                      |                 |                 |                 |
| subjects affected / exposed             | 1 / 16 (6.25%)  | 0 / 16 (0.00%)  | 0 / 16 (0.00%)  |
| occurrences (all)                       | 2               | 0               | 0               |
| Hyponatraemia                           |                 |                 |                 |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 2               | 1              |
| Diabetes Mellitus           |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hypercholesterolaemia       |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hyperglycaemia              |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hypernatraemia              |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hypoalbuminaemia            |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hypoglycaemia               |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hypokalaemia                |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 1               | 1              |
| Hypomagnesaemia             |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Iron Deficiency             |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Vitamin D Deficiency        |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Weight Fluctuation          |                |                 |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 16 (6.25%)  | 0 / 16 (0.00%) |
| occurrences (all)           | 0              | 1               | 0              |
| Hypercalcaemia              |                |                 |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 0              | 1              |
| Hypophosphataemia           |                |                |                |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all)           | 0              | 0              | 1              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 28 October 2013 | <p>Amendment 1</p> <ul style="list-style-type: none"><li>- Updated figure 1 Trial design to better reflect the design of the study.</li><li>- Replaced "treatment vials" with "treatment bottles" as the study drugs are tablets.</li><li>- Change of brain magnetic resonance imaging (MRI) from 4 weeks to 5 weeks before Day 1.</li><li>- Amendment and further clarification around the biopsies taken for this study as requested by The National Agency for the Safety of Medicines and Health Products (ANSM). This includes: a) That the biopsies were only to be done on cutaneous and subcutaneous lesions only if they are easily accessible; b) confirmation that no deep lesion biopsies were to be performed; c) clarification of who is qualified to perform the biopsies.</li><li>- Clarification regarding the confirmation of response.</li><li>- Clarification to the pharmacokinetic blood sampling.</li><li>- New France specific Appendix.</li><li>- Added to reflect the monitoring required for Cutaneous Squamous Cell Carcinoma (CuSCC), new primary melanoma and non- cutaneous secondary/recurrent malignancy as requested by ANSM. These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported