



## Clinical trial results:

**Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)**

### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2015-004015-20                   |
| Trial protocol           | GB SE CZ DE ES IT FI DK FR NL BE |
| Global end of trial date | 28 April 2023                    |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 11 November 2023 |
| First version publication date | 11 November 2023 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CDRB436G2201 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02684058 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 28 April 2023 |
| Is this the analysis of the primary completion data? | No            |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 28 April 2023 |
| Was the trial ended prematurely? | No            |

Notes:

## General information about the trial

Main objective of the trial:

LGG cohort: Compare the anti-tumor activity of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by Overall Response Rate (ORR) by central independent assessment using the Response Assessment in Neuro-Oncology (RANO) criteria.

HGG cohort: Evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by ORR by central independent assessment using the RANO criteria.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 28 December 2017 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Argentina: 3          |
| Country: Number of subjects enrolled | Australia: 11         |
| Country: Number of subjects enrolled | Belgium: 1            |
| Country: Number of subjects enrolled | Brazil: 6             |
| Country: Number of subjects enrolled | Canada: 5             |
| Country: Number of subjects enrolled | Czechia: 3            |
| Country: Number of subjects enrolled | Denmark: 5            |
| Country: Number of subjects enrolled | Finland: 2            |
| Country: Number of subjects enrolled | France: 11            |
| Country: Number of subjects enrolled | Germany: 17           |
| Country: Number of subjects enrolled | Israel: 2             |
| Country: Number of subjects enrolled | Italy: 21             |
| Country: Number of subjects enrolled | Japan: 17             |
| Country: Number of subjects enrolled | Netherlands: 5        |
| Country: Number of subjects enrolled | Russian Federation: 5 |
| Country: Number of subjects enrolled | Spain: 5              |
| Country: Number of subjects enrolled | Sweden: 4             |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Switzerland: 2    |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | United States: 21 |
| Worldwide total number of subjects   | 151               |
| EEA total number of subjects         | 74                |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 4  |
| Children (2-11 years)                     | 81 |
| Adolescents (12-17 years)                 | 66 |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in 58 centers across 20 countries

### Pre-assignment

Screening details:

Pediatric patients for both cohorts were screened for eligibility during the 28 days immediately prior to starting study treatment on Day 1.

In the HGG cohort, 46 patients were screened of whom 41 patients entered the HGG cohort

### Period 1

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 1 title               | Treatment period (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>             | LGG cohort: dabrafenib and trametinib |

Arm description:

Participants in the LGG cohort randomized to receive dabrafenib (orally, twice daily and dosed based on weight and age) in combination with trametinib (orally, once daily in combination with the first daily dose of dabrafenib and was dosed based on weight)

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

Dosage and administration details:

Dabrafenib was available as 50 mg and 75 mg hard capsules and as 10 mg dispersible tablets for oral suspension. Dabrafenib was administered orally, twice daily, and was dosed based on age and weight. Patients < 12 years old and  $\geq 16$  kg were to be administered either the dabrafenib capsules or dabrafenib dispersible tablets for oral suspension (dose: 5.25 mg/kg/day).

Patients  $\geq 12$  years old and  $\geq 19$  kg were to be administered either the dabrafenib capsules or dabrafenib dispersible tablets for oral suspension (dose: 4.5 mg/kg/day).

Patients < 12 years old and < 16 kg were to be administered dabrafenib dispersible tablets for oral suspension (dose: 5.25 mg/kg/day).

Patients  $\geq 12$  years old and < 19 kg were to be administered dabrafenib dispersible tablets for oral suspension (dose: 4.5 mg/kg/day).

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | Vincristine           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Vincristine was supplied locally as commercially available and labelled accordingly to comply with legal requirements of each country. Vincristine was administered as one course of induction (10 weeks of chemotherapy with 2 weeks of rest), followed by 8 cycles of maintenance chemotherapy.

Induction: 1.5 mg/m<sup>2</sup> as weekly IV bolus infusion (0.05 mg/kg if child is <12 kg) (maximum dose of 2.0 mg) for 10 weeks.

Maintenance: 1.5 mg/m<sup>2</sup> as weekly IV bolus infusion (0.05 mg/kg if child is <12 kg) (maximum dose of 2.0 mg) on weeks 1 to 3 of each cycle, on the same day as carboplatin dosing.

|  |  |
|--|--|
| Investigational medicinal product name | Trametinib                                     |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Film-coated tablet, Powder for oral suspension |
| Routes of administration               | Oral use                                       |

**Dosage and administration details:**

Trametinib was available as 0.5 mg and 2 mg film-coated tablets and as 5.0 mg powder in bottle for oral solution (0.05 mg/ml after reconstitution with 90 ml water). Trametinib was administered orally, once daily in combination with the first daily dose of dabrafenib and was dosed based on age and weight. Patients <6 years old and <26 kg were to be administered the trametinib oral solution (dose: 0.032 mg/kg/day)

Patients <6 years old and ≥26 kg were to be administered either the trametinib oral solution or trametinib tablets (dose: 0.032 mg/kg/day)

Patients ≥6 years old and ≥10 kg < 33 kg were to be administered the trametinib oral solution (dose: 0.025 mg/kg/day)

Patients ≥6 years old and ≥33 kg were to be administered either the trametinib oral solution or the trametinib tablets (dose: 0.025 mg/kg/day)

|                  |   |
|------------------|---|
| <b>Arm title</b> | LGG cohort: carboplatin and vincristine |
|------------------|---|

**Arm description:**

Participants in the LGG cohort randomized to receive active comparator chemotherapy (carboplatin and vincristine). Participants received one course of induction (10 weeks of chemotherapy with 2 weeks of rest), followed by 8 cycles of maintenance chemotherapy. Participants were allowed to crossover to dabrafenib and trametinib after centrally confirmed and RANO-defined disease progression.

|  |                       |
|--|-----------------------|
| Arm type                               | Active comparator     |
| Investigational medicinal product name | Carboplatin           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

**Dosage and administration details:**

Carboplatin was supplied locally as commercially available and labelled accordingly to comply with legal requirements of each country. Carboplatin was administered as one course of induction (10 weeks of chemotherapy with 2 weeks of rest), followed by 8 cycles of maintenance chemotherapy. Each maintenance cycle was 6 weeks, and consisted of 4 weeks of chemotherapy with 2 weeks of rest.

Induction: 175 mg/m<sup>2</sup> as weekly intravenous (IV) infusion on weeks 1 to 4, and on weeks 7 to 10, on the same day as vincristine dosing

Maintenance: 175 mg/m<sup>2</sup> as weekly IV infusion over 60 minutes on weeks 1 to 4 of each cycle.

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | HGG cohort: dabrafenib and trametinib |
|------------------|---------------------------------------|

**Arm description:**

Participants in the HGG cohort received dabrafenib (orally, twice daily and dosed based on weight and age) and trametinib (orally, once daily in combination with the first daily dose of dabrafenib and dosed based on weight)

|  |  |
|--|--|
| Arm type                               | Experimental                                   |
| Investigational medicinal product name | Trametinib                                     |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Film-coated tablet, Powder for oral suspension |
| Routes of administration               | Oral use                                       |

**Dosage and administration details:**

Trametinib was available as 0.5 mg and 2 mg film-coated tablets and as 5.0 mg powder in bottle for oral solution (0.05 mg/ml after reconstitution with 90 ml water). Trametinib was administered orally, once daily in combination with the first daily dose of dabrafenib and was dosed based on age and weight. Patients <6 years old and <26 kg were to be administered the trametinib oral solution (dose: 0.032 mg/kg/day)

Patients <6 years old and ≥26 kg were to be administered either the trametinib oral solution or trametinib tablets (dose: 0.032 mg/kg/day)

Patients ≥6 years old and ≥10 kg < 33 kg were to be administered the trametinib oral solution (dose: 0.025 mg/kg/day)

Patients ≥6 years old and ≥33 kg were to be administered either the trametinib oral solution or the trametinib tablets (dose: 0.025 mg/kg/day)

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | Dabrafenib                        |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Capsule, hard, Dispersible tablet |
| Routes of administration               | Oral use                          |

Dosage and administration details:

Dabrafenib was available as 50 mg and 75 mg hard capsules and as 10 mg dispersible tablets for oral suspension. Dabrafenib was administered orally, twice daily, and was dosed based on age and weight. Patients < 12 years old and ≥ 16 kg were to be administered either the dabrafenib capsules or dabrafenib dispersible tablets for oral suspension (dose: 5.25 mg/kg/day).

Patients ≥ 12 years old and ≥ 19 kg were to be administered either the dabrafenib capsules or dabrafenib dispersible tablets for oral suspension (dose: 4.5 mg/kg/day).

Patients < 12 years old and < 16 kg were to be administered dabrafenib dispersible tablets for oral suspension (dose: 5.25 mg/kg/day).

Patients ≥ 12 years old and < 19 kg were to be administered dabrafenib dispersible tablets for oral suspension (dose: 4.5 mg/kg/day).

| Number of subjects in period 1   | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine | HGG cohort:<br>dabrafenib and<br>trametinib |
|----------------------------------|---|---|---|
| Started                          | 73  | 37  | 41  |
| Treated                          | 73  | 33  | 41  |
| Completed                        | 56  | 14  | 17  |
| Not completed                    | 17  | 23  | 24  |
| Adverse event, serious fatal     | -   | -   | 2   |
| Physician decision               | 5   | 1   | 2   |
| Adverse event, non-fatal         | 3   | 8   | 1   |
| Protocol deviation               | -   | 1   | -   |
| Progressive disease              | 4   | 10  | 19  |
| New therapy for study indication | 1   | -   | -   |
| Subject/guardian decision        | 4   | 3   | -   |

## Baseline characteristics

### Reporting groups

|   |   |
|---|---|
| Reporting group title   | LGG cohort: dabrafenib and trametinib   |
| Reporting group description:  |   |
| Participants in the LGG cohort randomized to receive dabrafenib (orally, twice daily and dosed based on weight and age) in combination with trametinib (orally, once daily in combination with the first daily dose of dabrafenib and was dosed based on weight)  |   |
| Reporting group title   | LGG cohort: carboplatin and vincristine |
| Reporting group description:  |   |
| Participants in the LGG cohort randomized to receive active comparator chemotherapy (carboplatin and vincristine). Participants received one course of induction (10 weeks of chemotherapy with 2 weeks of rest), followed by 8 cycles of maintenance chemotherapy. Participants were allowed to crossover to dabrafenib and trametinib after centrally confirmed and RANO-defined disease progression. |   |
| Reporting group title   | HGG cohort: dabrafenib and trametinib   |
| Reporting group description:  |   |
| Participants in the HGG cohort received dabrafenib (orally, twice daily and dosed based on weight and age) and trametinib (orally, once daily in combination with the first daily dose of dabrafenib and dosed based on weight)   |   |

| Reporting group values     | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine | HGG cohort:<br>dabrafenib and<br>trametinib |
|----------------------------|---|---|---|
| Number of subjects         | 73  | 37  | 41  |
| Age Categorical            |   |   |   |
| Units: Participants        |   |   |   |
| <=18 years                 | 73  | 37  | 41  |
| Between 18 and 65 years    | 0   | 0   | 0   |
| >=65 years                 | 0   | 0   | 0   |
| Sex: Female, Male          |   |   |   |
| Units: Participants        |   |   |   |
| Female                     | 44  | 22  | 23  |
| Male                       | 29  | 15  | 18  |
| Race/Ethnicity, Customized |   |   |   |
| Units: Subjects            |   |   |   |
| White                      | 55  | 25  | 25  |
| Asian                      | 5   | 3   | 11  |
| Black Or African American  | 2   | 3   | 1   |
| Not Reported               | 2   | 1   | 1   |
| Unknown                    | 6   | 4   | 3   |
| Other                      | 3   | 1   | 0   |

| Reporting group values  | Total |  |  |
|-------------------------|-------|--|--|
| Number of subjects      | 151   |  |  |
| Age Categorical         |       |  |  |
| Units: Participants     |       |  |  |
| <=18 years              | 151   |  |  |
| Between 18 and 65 years | 0     |  |  |
| >=65 years              | 0     |  |  |

|                            |     |  |  |
|----------------------------|-----|--|--|
| Sex: Female, Male          |     |  |  |
| Units: Participants        |     |  |  |
| Female                     | 89  |  |  |
| Male                       | 62  |  |  |
| Race/Ethnicity, Customized |     |  |  |
| Units: Subjects            |     |  |  |
| White                      | 105 |  |  |
| Asian                      | 19  |  |  |
| Black Or African American  | 6   |  |  |
| Not Reported               | 4   |  |  |
| Unknown                    | 13  |  |  |
| Other                      | 4   |  |  |



## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | LGG cohort: dabrafenib and trametinib   |
| Reporting group description:<br>Participants in the LGG cohort randomized to receive dabrafenib (orally, twice daily and dosed based on weight and age) in combination with trametinib (orally, once daily in combination with the first daily dose of dabrafenib and was dosed based on weight)  |   |
| Reporting group title   | LGG cohort: carboplatin and vincristine |
| Reporting group description:<br>Participants in the LGG cohort randomized to receive active comparator chemotherapy (carboplatin and vincristine). Participants received one course of induction (10 weeks of chemotherapy with 2 weeks of rest), followed by 8 cycles of maintenance chemotherapy. Participants were allowed to crossover to dabrafenib and trametinib after centrally confirmed and RANO-defined disease progression. |   |
| Reporting group title   | HGG cohort: dabrafenib and trametinib   |
| Reporting group description:<br>Participants in the HGG cohort received dabrafenib (orally, twice daily and dosed based on weight and age) and trametinib (orally, once daily in combination with the first daily dose of dabrafenib and dosed based on weight)   |   |

### Primary: LGG cohort: Overall response rate (ORR) by central independent assessment using Response Assessment in Neuro-Oncology (RANO) criteria

|   |  |
|---|--|
| End point title   | LGG cohort: Overall response rate (ORR) by central independent assessment using Response Assessment in Neuro-Oncology (RANO) criteria <sup>[1]</sup> |
| End point description:<br>Percentage of participants in the LGG cohort with a best overall confirmed Complete Response (CR) or Partial Response (PR) as assessed per RANO criteria by central independent assessment. The 95% confidence intervals (CIs) were computed using two-sided exact binomial method.<br>CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.<br>PR: $\geq 50\%$ reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically. |  |
| End point type  | Primary  |
| End point timeframe:<br>Up to approximately (approx.) 3 years   |  |

#### Notes:

[1] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                  | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed       | 73  | 37  |  |  |
| Units: Percentage of participants |   |   |  |  |
| number (confidence interval 95%)  | 46.6 (34.8 to 58.6)                         | 10.8 (3.0 to 25.4)                            |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | LGG cohort: ORR analysis  |
| Comparison groups                       | LGG cohort: dabrafenib and trametinib v LGG cohort: carboplatin and vincristine |
| Number of subjects included in analysis | 110   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[2]</sup>  |
| P-value                                 | < 0.001   |
| Method                                  | Chi-squared   |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 7.19  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 2.3   |
| upper limit                             | 22.4  |

Notes:

[2] - one-sided p-value at 2.5% level of significance

## Primary: HGG cohort: Overall response rate (ORR) by central independent assessment using RANO criteria

|  |   |
|--|---|
| End point title  | HGG cohort: Overall response rate (ORR) by central independent assessment using RANO criteria <sup>[3][4]</sup> |
| End point description:   |   |
| Percentage of participants in the HGG cohort with a best overall confirmed CR or PR as assessed per RANO criteria by central independent assessment. The 95% CIs were computed using two-sided exact binomial method.<br>CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.<br>PR: ≥ 50% reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically. |   |
| End point type   | Primary   |

End point timeframe:

Up to approx. 3.2 years

Notes:

[3] - 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: This endpoint is reporting results for the HGG cohort arm

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

Justification: This endpoint is reporting results for the HGG cohort arm

|                                   |   |  |  |  |
|-----------------------------------|---|--|--|--|
| <b>End point values</b>           | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |  |
| Subject group type                | Reporting group                             |  |  |  |
| Number of subjects analysed       | 41  |  |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (confidence interval 95%)  | 56.1 (39.7 to<br>71.5)                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LGG cohort: ORR by investigator assessment using RANO criteria

|                 |   |
|-----------------|---|
| End point title | LGG cohort: ORR by investigator assessment using RANO criteria <sup>[5]</sup> |
|-----------------|---|

End point description:

Percentage of participants in the LGG cohort with a best overall confirmed CR or PR as assessed per RANO criteria by investigator assessment. The 95% CIs were computed using two-sided exact binomial method.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

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

End point timeframe:

Up to approx. 3 years and up to approx 4.2 years

Notes:

[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: This endpoint is reporting results for LGG cohort arms

|                                   |   |   |  |  |
|-----------------------------------|---|---|--|--|
| <b>End point values</b>           | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
| Subject group type                | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed       | 73  | 37  |  |  |
| Units: Percentage of participants |   |   |  |  |
| number (confidence interval 95%)  |   |   |  |  |
| Up to approx. 3 years             | 54.8 (42.7 to<br>66.5)                      | 13.5 (4.5 to<br>28.8)                         |  |  |
| Up to approx. 4.2 years           | 58.9 (46.8 to<br>70.3)                      | 18.9 (8.0 to<br>35.2)                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LGG cohort: Kaplan-Meier Estimates of Duration of Response (DOR) as

## per Central Independent Assessment using RANO Criteria

|                 |   |
|-----------------|---|
| End point title | LGG cohort: Kaplan-Meier Estimates of Duration of Response (DOR) as per Central Independent Assessment using RANO Criteria <sup>[6]</sup> |
|-----------------|---|

### End point description:

Time from first documented response (PR or CR) until disease progression or death as per RANO criteria. CIs were estimated using the Brookmeyer Crowley method. Patients who had not progressed or died or had received further anticancer therapy, were censored at the date of the last adequate tumor evaluation.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

9999= value was not estimable.

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

### End point timeframe:

Up to approx. 3 years and up to approx 4.2 years

### Notes:

[6] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                 | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed      | 40  | 6   |  |  |
| Units: Months                    |   |   |  |  |
| median (confidence interval 95%) |   |   |  |  |
| Up to approx. 3 years            | 20.3 (12.0 to 9999)                         | 9999 (6.6 to 9999)                            |  |  |
| Up to approx 4.2 years           | 30.0 (16.6 to 9999)                         | 19.4 (6.6 to 9999)                            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LGG cohort: Kaplan-Meier Estimates of Duration of Response (DOR) as per Investigator Assessment using RANO Criteria

|                 |  |
|-----------------|--|
| End point title | LGG cohort: Kaplan-Meier Estimates of Duration of Response (DOR) as per Investigator Assessment using RANO Criteria <sup>[7]</sup> |
|-----------------|--|

### End point description:

Time from first documented response (PR or CR) until disease progression or death as per RANO criteria. CIs were estimated using the Brookmeyer Crowley method. Patients who had not progressed or died or had received further anticancer therapy, were censored at the date of the last adequate tumor evaluation.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

9999 = value was not estimable.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Up to approx. 3 years and up to approx 4.2 years  |           |
| Notes:  |           |
| [7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. |           |
| Justification: This endpoint is reporting results for LGG cohort arms   |           |

| End point values                 | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed      | 43  | 7   |  |  |
| Units: Months                    |   |   |  |  |
| median (confidence interval 95%) |   |   |  |  |
| Up to approx. 3 years            | 9999 (25.5 to 9999)                         | 9999 (5.3 to 9999)                            |  |  |
| Up to approx 4.2 years           | 44.4 (33.1 to 9999)                         | 22.5 (5.3 to 9999)                            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LGG cohort: Kaplan-Meier Progression-Free Survival (PFS) as per Central Independent Assessment using RANO Criteria

|   |   |
|---|---|
| End point title   | LGG cohort: Kaplan-Meier Progression-Free Survival (PFS) as per Central Independent Assessment using RANO Criteria <sup>[8]</sup> |
| End point description:  |   |
| Time from the date of randomization to the date of first documented disease progression as per central independent review assessment using RANO criteria or death due to any cause. Confidence Intervals were estimated using the Brookmeyer Crowley method. Patients who had not progressed or died or had received further anticancer therapy were censored at the date of the last adequate tumor evaluation. 9999 indicates that the value was not estimable. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Up to approx. 3 years and up to approx 4.2 years  |   |
| Notes:  |   |

[8] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                 | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed      | 73  | 37  |  |  |
| Units: Months                    |   |   |  |  |
| median (confidence interval 95%) |   |   |  |  |
| Up to approx. 3 years            | 20.1 (12.8 to 9999)                         | 7.4 (3.6 to 11.8)                             |  |  |
| Up to approx 4.2 years           | 24.9 (12.9 to 31.6)                         | 7.2 (2.8 to 11.2)                             |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>                          | LGG cohort: PFS analysis  |
| Statistical analysis description:<br>Up to approx. 3 years |   |
| Comparison groups  | LGG cohort: dabrafenib and trametinib v LGG cohort: carboplatin and vincristine |
| Number of subjects included in analysis                    | 110   |
| Analysis specification                                     | Pre-specified   |
| Analysis type  |   |
| P-value  | < 0.001 <sup>[9]</sup>  |
| Method   | Logrank   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.31  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.17  |
| upper limit  | 0.55  |

Notes:

[9] - Log-rank test at an overall one-sided 2.5% level of significance

## Secondary: LGG cohort: Kaplan-Meier Progression-Free Survival (PFS) as per Investigator Assessment using RANO Criteria

|   |   |
|---|---|
| End point title   | LGG cohort: Kaplan-Meier Progression-Free Survival (PFS) as per Investigator Assessment using RANO Criteria <sup>[10]</sup> |
| End point description:<br>Time from the date of randomization to the date of first documented disease progression as per investigator assessment using RANO criteria or death due to any cause. Confidence Intervals were estimated using the Brookmeyer Crowley method. Patients who had not progressed or died or had received further anticancer therapy were censored at the date of the last adequate tumor evaluation. 9999 indicates that the value was not estimable. |   |
| End point type  | Secondary   |

End point timeframe:

Up to approx. 3 years and up to approx 4.2 years

Notes:

[10] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                 | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed      | 73  | 37  |  |  |
| Units: Months                    |   |   |  |  |
| median (confidence interval 95%) |   |   |  |  |
| Up to approx. 3 years            | 9999 (-9999 to<br>9999)                     | 9999 (12.6 to<br>9999)                        |  |  |
| Up to approx 4.2 years           | 46.0 (38.6 to<br>9999)                      | 30.8 (7.0 to<br>9999)                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LGG cohort: Kaplan-Meier Estimates of Time to Response (TTR) as per Central Independent Assessment using RANO Criteria

|                 |  |
|-----------------|--|
| End point title | LGG cohort: Kaplan-Meier Estimates of Time to Response (TTR) as per Central Independent Assessment using RANO Criteria <sup>[11]</sup> |
|-----------------|--|

End point description:

Time from randomization to first documented response (CR or PR) as per central independent assessment using RANO criteria. Patients without an event were censored either at the maximum follow-up time (if they experienced disease progression or death), or at their last tumor assessment date. CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses. PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.  
9999 = value was not estimable

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

End point timeframe:

Up to approx. 4.2 years

Notes:

[11] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                 | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed      | 73  | 37  |  |  |
| Units: Months                    |   |   |  |  |
| median (confidence interval 95%) | 11.0 (6.0 to<br>9999)                       | 9999 (-9999 to<br>9999)                       |  |  |

## Statistical analyses

**Secondary: LGG cohort: Kaplan-Meier Estimates of Time to Response (TTR) as per Investigator Assessment using RANO Criteria**

|                 |   |
|-----------------|---|
| End point title | LGG cohort: Kaplan-Meier Estimates of Time to Response (TTR) as per Investigator Assessment using RANO Criteria <sup>[12]</sup> |
|-----------------|---|

## End point description:

Time from randomization to first documented response (CR or PR) as per central independent assessment using RANO criteria. Patients without an event were censored either at the maximum follow-up time (if they experienced disease progression or death), or at their last tumor assessment date. CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses. PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

9999 = value was not estimable

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

## End point timeframe:

Up to approx. 4.2 years

## Notes:

[12] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                 | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|----------------------------------|---|---|--|--|
| Subject group type               | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed      | 73  | 37  |  |  |
| Units: Months                    |   |   |  |  |
| median (confidence interval 95%) | 7.4 (5.3 to 9999)                           | 9999 (-9999 to 9999)                          |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: LGG cohort: Clinical Benefit Rate (CBR) by central independent assessment using RANO criteria**

|                 |   |
|-----------------|---|
| End point title | LGG cohort: Clinical Benefit Rate (CBR) by central independent assessment using RANO criteria <sup>[13]</sup> |
|-----------------|---|

## End point description:

Percentage of participants with a best overall response of CR or PR, or stable disease (SD) which lasts for 24 weeks or longer.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

SD: Patient did not qualify for CR, PR, or progressive disease and has stable nonenhancing (T2/FLAIR) lesions on same or lower doses of corticosteroids compared with baseline scan and clinically stable status.



|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Up to approx. 4.2 years  |           |
| Notes:   |           |
| [13] - 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: This endpoint is reporting results for LGG cohort arms  |           |

| End point values                  | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed       | 73  | 37  |  |  |
| Units: Percentage of participants |   |   |  |  |
| number (confidence interval 95%)  | 86.3 (76.2 to 93.2)                         | 43.2 (27.1 to 60.5)                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LGG cohort: Clinical Benefit Rate (CBR) by investigator assessment using RANO criteria

|                 |  |
|-----------------|--|
| End point title | LGG cohort: Clinical Benefit Rate (CBR) by investigator assessment using RANO criteria <sup>[14]</sup> |
|-----------------|--|

End point description:

Percentage of participants with a best overall response of CR or PR, or stable disease (SD) which lasts for 24 weeks or longer.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

SD: Patient did not qualify for CR, PR, or progressive disease and has stable nonenhancing (T2/FLAIR) lesions on same or lower doses of corticosteroids compared with baseline scan and clinically stable status.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Up to approx. 4.2 years  |           |
| Notes:   |           |
| [14] - 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: This endpoint is reporting results for LGG cohort arms  |           |

| End point values                  | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed       | 73  | 37  |  |  |
| Units: Percentage of participants |   |   |  |  |
| number (confidence interval 95%)  | 91.8 (83.0 to 96.9)                         | 56.8 (39.5 to 72.9)                           |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: LGG cohort: Kaplan-Meier Estimates of Overall survival (OS)

|                 |   |
|-----------------|---|
| End point title | LGG cohort: Kaplan-Meier Estimates of Overall survival (OS) <sup>[15]</sup> |
|-----------------|---|

End point description:

Time from first dose to death due to any cause in the LGG cohort. Confidence Intervals were estimated using the Brookmeyer Crowley method. If a patient was not known to have died at the time of analysis cut-off, OS was censored at the date of last contact.

9999 indicates that the value was not estimable.

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

End point timeframe:

Up to 4.6 years

Notes:

[15] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                 | LGG cohort: dabrafenib and trametinib | LGG cohort: carboplatin and vincristine |  |  |
|----------------------------------|---------------------------------------|---|--|--|
| Subject group type               | Reporting group                       | Reporting group                         |  |  |
| Number of subjects analysed      | 73                                    | 37                                      |  |  |
| Units: Months                    |                                       |   |  |  |
| median (confidence interval 95%) | 9999 (-9999 to 9999)                  | 9999 (-9999 to 9999)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: LGG cohort: 2-year OS estimate

|                 |  |
|-----------------|--|
| End point title | LGG cohort: 2-year OS estimate <sup>[16]</sup> |
|-----------------|--|

End point description:

OS was defined as the time from the first dose to death due to any cause in the LGG cohort. The 2-year Kaplan-Meier OS estimate represented the estimated percentage of participants remaining free from OS events for up to 2 years. If a patient was not known to have died at the time of analysis cut-off, OS was censored at the date of last contact

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

End point timeframe:

2 years from first dose

Notes:

[16] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                  | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed       | 73  | 37  |  |  |
| Units: Percentage of participants |   |   |  |  |
| number (confidence interval 95%)  | 100.0 (100.0<br>to 100.0)                   | 96.9 (79.8 to<br>99.6)                        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG cohort: ORR by investigator assessment using RANO criteria

|                 |  |
|-----------------|--|
| End point title | HGG cohort: ORR by investigator assessment using RANO criteria <sup>[17]</sup> |
|-----------------|--|

End point description:

ORR in the HGG cohort defined as the percentage of participants in the HGG cohort with a best overall confirmed CR or PR as assessed per RANO criteria by investigator assessment. The 95% CIs were computed using two-sided exact binomial method.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

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

End point timeframe:

Up to approx. 3.2 years and up to approx. 4.8 years

Notes:

[17] - 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: This endpoint is reporting results for the HGG cohort arm

| End point values                  | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group                             |  |  |  |
| Number of subjects analysed       | 41  |  |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (confidence interval 95%)  |   |  |  |  |
| Up to approx. 3.2 years           | 58.5 (42.1 to<br>73.7)                      |  |  |  |
| Up to approx. 4.8 years           | 61.0 (44.5 to<br>75.8)                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: HGG cohort: Kaplan-Meier Estimates of Duration of Response (DOR) as per Central Independent Assessment using RANO Criteria

|                 |  |
|-----------------|--|
| End point title | HGG cohort: Kaplan-Meier Estimates of Duration of Response (DOR) as per Central Independent Assessment using RANO Criteria <sup>[18]</sup> |
|-----------------|--|

#### End point description:

Time from first documented response (PR or CR) until disease progression or death as per central independent assessment using RANO criteria. Patients who had not progressed or died or had received further anticancer therapy were censored at the date of the last adequate tumor evaluation.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

9999=value was not estimable.

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

#### End point timeframe:

Up to approx. 3.2 years and up to approx. 4.8 years

#### Notes:

[18] - 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: This endpoint is reporting results for the HGG cohort arm

|                                  |                                       |  |  |  |
|----------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>          | HGG cohort: dabrafenib and trametinib |  |  |  |
| Subject group type               | Reporting group                       |  |  |  |
| Number of subjects analysed      | 23                                    |  |  |  |
| Units: Months                    |                                       |  |  |  |
| median (confidence interval 95%) |                                       |  |  |  |
| Up to approx. 3.2 years          | 22.2 (7.6 to 9999)                    |  |  |  |
| Up to approx. 4.8 years          | 27.4 (9.2 to 9999)                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: HGG cohort: Kaplan-Meier Estimates of Duration of Response (DOR) as per Investigator Assessment using RANO Criteria

|                 |   |
|-----------------|---|
| End point title | HGG cohort: Kaplan-Meier Estimates of Duration of Response (DOR) as per Investigator Assessment using RANO Criteria <sup>[19]</sup> |
|-----------------|---|

End point description:

Time from first documented response (PR or CR) until disease progression or death as per investigator assessment using RANO criteria. Patients who had not progressed or died or had received further anticancer therapy were censored at the date of the last adequate tumor evaluation.  
CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.  
PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.  
9999= value was not estimable.

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

End point timeframe:

Up to approx. 3.2 years and up to approx. 4.8 years

Notes:

[19] - 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: This endpoint is reporting results for the HGG cohort arm

| End point values                 | HGG cohort: dabrafenib and trametinib |  |  |  |
|----------------------------------|---------------------------------------|--|--|--|
| Subject group type               | Reporting group                       |  |  |  |
| Number of subjects analysed      | 25                                    |  |  |  |
| Units: Months                    |                                       |  |  |  |
| median (confidence interval 95%) |                                       |  |  |  |
| Up to approx. 3.2 years          | 26.6 (14.9 to 9999)                   |  |  |  |
| Up to approx. 4.8 years          | 32.7 (14.9 to 9999)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG cohort: Kaplan-Meier Estimates of Progression free survival (PFS) as per Central Independent Assessment using RANO Criteria

|                 |   |
|-----------------|---|
| End point title | HGG cohort: Kaplan-Meier Estimates of Progression free survival (PFS) as per Central Independent Assessment using RANO Criteria <sup>[20]</sup> |
|-----------------|---|

End point description:

Time from the date of first dose of study treatment to the date of first documented disease progression as per central independent review assessment using RANO criteria or death due to any cause. Confidence Intervals were estimated using the Brookmeyer Crowley method. Patients who had not progressed or died or had received further anticancer therapy were censored at the date of the last adequate tumor evaluation.

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

End point timeframe:

Up to approx. 4.8 years

Notes:

[20] - 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: This endpoint is reporting results for the HGG cohort arm

|                                  |   |  |  |  |
|----------------------------------|---|--|--|--|
| <b>End point values</b>          | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |  |
| Subject group type               | Reporting group                             |  |  |  |
| Number of subjects analysed      | 41  |  |  |  |
| Units: Months                    |   |  |  |  |
| median (confidence interval 95%) | 9.0 (5.3 to<br>20.1)                        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG cohort: Time to response (TTR) as per Central Independent Assessment using RANO Criteria

|                 |  |
|-----------------|--|
| End point title | HGG cohort: Time to response (TTR) as per Central Independent Assessment using RANO Criteria <sup>[21]</sup> |
|-----------------|--|

End point description:

Time from start of treatment to first documented response of CR or PR as per independent assessment using RANO criteria. Patients without an event were censored either at the maximum follow-up time (if they experienced disease progression or death), or at their last tumor assessment date.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

9999= value was not estimable.

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

End point timeframe:

Up to approx. 4.8 years

Notes:

[21] - 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: This endpoint is reporting results for the HGG cohort arm

|                                  |   |  |  |  |
|----------------------------------|---|--|--|--|
| <b>End point values</b>          | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |  |
| Subject group type               | Reporting group                             |  |  |  |
| Number of subjects analysed      | 41  |  |  |  |
| Units: Months                    |   |  |  |  |
| median (confidence interval 95%) | 8.5 (2.0 to<br>9999)                        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: HGG cohort: Kaplan-Meier Estimates of Progression free survival (PFS) as per Investigator Assessment using RANO Criteria

|                 |  |
|-----------------|--|
| End point title | HGG cohort: Kaplan-Meier Estimates of Progression free survival (PFS) as per Investigator Assessment using RANO Criteria <sup>[22]</sup> |
|-----------------|--|

End point description:

Time from the date of first dose of study treatment to the date of first documented disease progression as per investigator assessment using RANO criteria or death due to any cause. Confidence Intervals were estimated using the Brookmeyer Crowley method. Patients who had not progressed or died or had received further anticancer therapy were censored at the date of the last adequate tumor evaluation. 9999 indicates that the value was not estimable.

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

End point timeframe:

Up to approx. 4.8 years

Notes:

[22] - 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: This endpoint is reporting results for the HGG cohort arm

|                                  |                                       |  |  |  |
|----------------------------------|---------------------------------------|--|--|--|
| <b>End point values</b>          | HGG cohort: dabrafenib and trametinib |  |  |  |
| Subject group type               | Reporting group                       |  |  |  |
| Number of subjects analysed      | 41                                    |  |  |  |
| Units: Months                    |                                       |  |  |  |
| median (confidence interval 95%) | 24.0 (12.5 to 9999)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: HGG Cohort: Clinical benefit rate (CBR) as per Central Independent Assessment using RANO Criteria

|                 |   |
|-----------------|---|
| End point title | HGG Cohort: Clinical benefit rate (CBR) as per Central Independent Assessment using RANO Criteria <sup>[23]</sup> |
|-----------------|---|

End point description:

Percentage of participants with a best overall response of CR or PR, or stable disease (SD) which lasts for 24 weeks or longer.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

SD: Patient did not qualify for CR, PR, or progressive disease and has stable nonenhancing (T2/FLAIR) lesions on same or lower doses of corticosteroids compared with baseline scan and clinically stable status.

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

End point timeframe:

Up to approx. 4.8 years

Notes:

[23] - 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: This endpoint is reporting results for the HGG cohort arm

|                                   |   |  |  |  |
|-----------------------------------|---|--|--|--|
| <b>End point values</b>           | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |  |
| Subject group type                | Reporting group                             |  |  |  |
| Number of subjects analysed       | 41  |  |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (confidence interval 95%)  | 65.9 (49.4 to<br>79.9)                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG cohort: Time to response (TTR) as per Investigator Assessment using RANO Criteria

|                 |   |
|-----------------|---|
| End point title | HGG cohort: Time to response (TTR) as per Investigator Assessment using RANO Criteria <sup>[24]</sup> |
|-----------------|---|

End point description:

Time from start of treatment to first documented response of CR or PR as per investigator assessment using RANO criteria. Patients without an event were censored either at the maximum follow-up time (if they experienced disease progression or death), or at their last tumor assessment date.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR: ≥ 50% reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

9999 = value was not estimable

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

End point timeframe:

Up to approx. 4.8 years

Notes:

[24] - 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: This endpoint is reporting results for the HGG cohort arm

|                                  |   |  |  |  |
|----------------------------------|---|--|--|--|
| <b>End point values</b>          | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |  |
| Subject group type               | Reporting group                             |  |  |  |
| Number of subjects analysed      | 41  |  |  |  |
| Units: Months                    |   |  |  |  |
| median (confidence interval 95%) | 3.4 (1.8 to<br>9999)                        |  |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: HGG Cohort: Clinical benefit rate (CBR) as per Investigator Assessment using RANO Criteria

|                 |  |
|-----------------|--|
| End point title | HGG Cohort: Clinical benefit rate (CBR) as per Investigator Assessment using RANO Criteria <sup>[25]</sup> |
|-----------------|--|

End point description:

Percentage of participants with a best overall response of CR or PR, or stable disease (SD) which lasts for 24 weeks or longer.

CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses.

PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically.

SD: Patient did not qualify for CR, PR, or progressive disease and has stable nonenhancing (T2/FLAIR) lesions on same or lower doses of corticosteroids compared with baseline scan and clinically stable status.

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

End point timeframe:

Up to approx. 4.8 years

Notes:

[25] - 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: This endpoint is reporting results for the HGG cohort arm

|                                   |                                       |  |  |  |
|-----------------------------------|---------------------------------------|--|--|--|
| End point values                  | HGG cohort: dabrafenib and trametinib |  |  |  |
| Subject group type                | Reporting group                       |  |  |  |
| Number of subjects analysed       | 41                                    |  |  |  |
| Units: Percentage of participants |                                       |  |  |  |
| number (confidence interval 95%)  | 75.6 (59.7 to 87.6)                   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: AUClast for trametinib

|                 |  |
|-----------------|--|
| End point title | AUClast for trametinib <sup>[26]</sup> |
|-----------------|--|

End point description:

Pharmacokinetic (PK) parameters were calculated by standard non-compartmental analysis. AUClast is the area under the curve (AUC) from time zero to the last measurable concentration sampling time

(tlast).

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

End point timeframe:

Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose

Notes:

[26] - 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: This endpoint is reporting results for all arms receiving trametinib

|  |   |   |  |  |
|--|---|---|--|--|
| <b>End point values</b>                                | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
| Subject group type                                     | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                            | 55  | 36  |  |  |
| Units: hour (hr) * nanogram<br>(ng)/milliliter (mL)    |   |   |  |  |
| geometric mean (geometric coefficient<br>of variation) | 328 ( $\pm$ 33.4)                           | 282 ( $\pm$ 53.7)                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG cohort: Kaplan-Meier Estimates of Overall survival (OS)

|                 |   |
|-----------------|---|
| End point title | HGG cohort: Kaplan-Meier Estimates of Overall survival (OS) <sup>[27]</sup> |
|-----------------|---|

End point description:

Time from first dose to death due to any cause in the LGG cohort. Confidence Intervals were estimated using the Brookmeyer Crowley method. If a patient was not known to have died at the time of analysis cut-off, OS was censored at the date of last contact.

9999 indicates that the value was not estimable

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

End point timeframe:

Up to 5.1 years

Notes:

[27] - 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: This endpoint is reporting results for the HGG cohort arm

|                                  |   |  |  |  |
|----------------------------------|---|--|--|--|
| <b>End point values</b>          | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |  |
| Subject group type               | Reporting group                             |  |  |  |
| Number of subjects analysed      | 41  |  |  |  |
| Units: Months                    |   |  |  |  |
| median (confidence interval 95%) | 9999 (19.8 to<br>9999)                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Cmax for trametinib

|  |                                     |
|--|-------------------------------------|
| End point title  | Cmax for trametinib <sup>[28]</sup> |
| End point description:<br>PK parameters were calculated by standard non-compartmental analysis. Cmax is the maximum plasma drug concentration after single dose administration |                                     |
| End point type   | Secondary                           |
| End point timeframe:<br>Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose  |                                     |

Notes:

[28] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 55  | 36  |  |  |
| Units: ng/mL  |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 22.7 (± 41.1)                               | 21.3 (± 36.3)                               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: AUCtau for trametinib

|  |                                       |
|--|---------------------------------------|
| End point title  | AUCtau for trametinib <sup>[29]</sup> |
| End point description:<br>PK parameters were calculated by standard non-compartmental analysis. AUCtau is the AUC calculated to the end of a dosing interval (tau) at steady-state |                                       |
| End point type   | Secondary                             |
| End point timeframe:<br>Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose  |                                       |

Notes:

[29] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 44  | 33  |  |  |
| Units: hr * ng/mL                                   |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 339 (± 22.2)                                | 307 (± 22.8)                                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Tmax for trametinib

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Tmax for trametinib <sup>[30]</sup> |
|-----------------|-------------------------------------|

End point description:

PK parameters were calculated by standard non-compartmental analysis. Tmax is the time to reach maximum plasma concentration. Actual recorded sampling times were considered for the calculations.

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

End point timeframe:

Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose

Notes:

[30] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 55  | 36  |  |  |
| Units: hour   |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 1.53 (± 54.6)                               | 1.67 (± 58.1)                               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: T1/2 for trametinib

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | T1/2 for trametinib <sup>[31]</sup> |
|-----------------|-------------------------------------|

End point description:

PK parameters were calculated by standard non-compartmental analysis. T1/2 is the elimination half-life

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

End point timeframe:

Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose

Notes:

[31] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 14  | 24  |  |  |
| Units: hour   |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 25.7 ( $\pm$ 37.9)                          | 26.7 ( $\pm$ 62.6)                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Ctrough for trametinib

|  |  |
|--|--|
| End point title  | Ctrough for trametinib <sup>[32]</sup> |
| End point description:<br>PK parameters were calculated by standard non-compartmental analysis. Ctrough is the pre-dose plasma concentration |  |
| End point type   | Secondary                              |
| End point timeframe:<br>Week 3 Day 1 pre-dose  |  |

Notes:

[32] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 55  | 36  |  |  |
| Units: ng/ml  |   |   |  |  |
| geometric mean (geometric coefficient of variation) | 9.82 ( $\pm$ 30.1)                          | 8.73 ( $\pm$ 72.7)                          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: AUClast for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib)

|  |  |
|--|--|
| End point title  | AUClast for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib) <sup>[33]</sup> |
| End point description:<br>PK parameters were calculated by standard non-compartmental analysis. AUClast is the area under the curve (AUC) from time zero to the last measurable concentration sampling time (tlast). |  |
| End point type   | Secondary  |
| End point timeframe:<br>Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose  |  |

Notes:

[33] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 54  | 34  |  |  |
| Units: hr * ng/ml                                   |   |   |  |  |
| geometric mean (geometric coefficient of variation) |   |   |  |  |
| Dabrafenib  | 4870 (± 60.3)                               | 4330 (± 44.7)                               |  |  |
| Carboxy-dabrafenib                                  | 64200 (± 46.9)                              | 73400 (± 31.5)                              |  |  |
| Desmethyl-dabrafenib                                | 3870 (± 68.2)                               | 3520 (± 60.2)                               |  |  |
| Hydroxy-dabrafenib                                  | 2980 (± 50.1)                               | 2810 (± 36.5)                               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib)

|                 |   |
|-----------------|---|
| End point title | Cmax for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib) <sup>[34]</sup> |
|-----------------|---|

End point description:

PK parameters were calculated by standard non-compartmental analysis. Cmax is the maximum plasma drug concentration after single dose administration

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

End point timeframe:

Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose

Notes:

[34] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 54  | 34  |  |  |
| Units: ng/ml  |   |   |  |  |
| geometric mean (geometric coefficient of variation) |   |   |  |  |
| Dabrafenib  | 1330 (± 93.5)                               | 1520 (± 65.9)                               |  |  |
| Carboxy-dabrafenib                                  | 7210 (± 51.6)                               | 9050 (± 31.4)                               |  |  |
| Desmethyl-dabrafenib                                | 377 (± 67.2)                                | 388 (± 67.2)                                |  |  |
| Hydroxy-dabrafenib                                  | 687 (± 82.6)                                | 801 (± 58.8)                                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: AUCtau for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib)

|                 |   |
|-----------------|---|
| End point title | AUCtau for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib) <sup>[35]</sup> |
|-----------------|---|

End point description:

PK parameters were calculated by standard non-compartmental analysis. AUCtau is the AUC calculated to the end of a dosing interval (tau) at steady-state

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

End point timeframe:

Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose

Notes:

[35] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 47  | 34  |  |  |
| Units: hr * ng/ml                                   |   |   |  |  |
| geometric mean (geometric coefficient of variation) |   |   |  |  |
| Dabrafenib (n= 34 / 47)                             | 4910 (± 54.0)                               | 4300 (± 44.7)                               |  |  |
| Carboxy-dabrafenib (n= 29 / 47)                     | 60700 (± 45.7)                              | 71200 (± 34.0)                              |  |  |
| Desmethyl-dabrafenib (n= 27 / 44)                   | 3660 (± 66.9)                               | 3360 (± 57.7)                               |  |  |
| Hydroxy-dabrafenib (n= 33 / 47)                     | 2960 (± 47.4)                               | 2840 (± 35.7)                               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Tmax for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib)

|                 |   |
|-----------------|---|
| End point title | Tmax for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib) <sup>[36]</sup> |
|-----------------|---|

End point description:

PK parameters were calculated by standard non-compartmental analysis. Tmax is the time to reach maximum plasma concentration. Actual recorded sampling times were considered for the calculations.

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

End point timeframe:

Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose

Notes:

[36] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 54  | 34  |  |  |
| Units: hr   |   |   |  |  |
| geometric mean (geometric coefficient of variation) |   |   |  |  |
| Dabrafenib  | 1.47 (± 52.9)                               | 1.47 (± 54.2)                               |  |  |
| Carboxy-dabrafenib                                  | 3.66 (± 51.4)                               | 3.37 (± 35.4)                               |  |  |
| Desmethyl-dabrafenib                                | 2.29 (± 82.0)                               | 2.21 (± 76.7)                               |  |  |
| Hydroxy-dabrafenib                                  | 1.68 (± 57.8)                               | 1.97 (± 45.9)                               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: T1/2 for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib)

|                 |   |
|-----------------|---|
| End point title | T1/2 for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib and hydroxy-dabrafenib) <sup>[37]</sup> |
|-----------------|---|

End point description:

PK parameters were calculated by standard non-compartmental analysis. T1/2 is the elimination half-life.

9999 indicates that the value was not estimable.

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

End point timeframe:

Week 3 Day 1 pre-dose and 0.5, 1, 2, 3, 4, 6, 8 hours post-dose

Notes:

[37] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 18  | 33  |  |  |
| Units: hr   |   |   |  |  |
| geometric mean (geometric coefficient of variation) |   |   |  |  |
| Dabrafenib (n= 33 / 18)                             | 3.09 (± 36.4)                               | 2.48 (± 36.6)                               |  |  |
| Carboxy-dabrafenib (n= 20 / 8)                      | 6.59 (± 43.9)                               | 7.12 (± 32.3)                               |  |  |
| Desmethyl-dabrafenib (n= 3 / 1)                     | 16.1 (± 9999)                               | 7.06 (± 392.5)                              |  |  |



|                                 |               |               |  |  |
|---------------------------------|---------------|---------------|--|--|
| Hydroxy-dabrafenib (n= 20 / 10) | 3.52 (± 71.7) | 2.66 (± 47.8) |  |  |
|---------------------------------|---------------|---------------|--|--|

## Statistical analyses

No statistical analyses for this end point

### Secondary: Ctrough for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib amd hydroxy-dabrafenib)

|                 |  |
|-----------------|--|
| End point title | Ctrough for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib amd hydroxy-dabrafenib) <sup>[38]</sup> |
|-----------------|--|

End point description:

PK parameters were calculated by standard non-compartmental analysis. Ctrough is the pre-dose plasma concentration

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

End point timeframe:

Week 3 Day 1 pre-dose

Notes:

[38] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                    | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|---|---|---|--|--|
| Subject group type                                  | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                         | 54  | 34  |  |  |
| Units: ng/ml  |   |   |  |  |
| geometric mean (geometric coefficient of variation) |   |   |  |  |
| Dabrafenib  | 46.0 (± 125.1)                              | 38.0 (± 162.0)                              |  |  |
| Carboxy-dabrafenib                                  | 3190 (± 54.4)                               | 3980 (± 46.1)                               |  |  |
| Desmethyl-dabrafenib                                | 310 (± 70.1)                                | 275 (± 116.5)                               |  |  |
| Hydroxy-dabrafenib                                  | 44.3 (± 99.7)                               | 41.8 (± 123.8)                              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: HGG and LGG cohort: Palatability of dabrafenib oral suspension based on the palatability questionnaire item: taste of the medication before rinsing the mouth

|                 |   |
|-----------------|---|
| End point title | HGG and LGG cohort: Palatability of dabrafenib oral suspension based on the palatability questionnaire item: taste of the medication before rinsing the mouth <sup>[39]</sup> |
|-----------------|---|

End point description:

Participants who received the dabrafenib dispersible tablets for oral suspension completed a questionnaire to evaluate the palatability of the pediatric formulation. After taking the medication, participants provided feedback on how it tasted before rinsing with water, rating their experience as very good, good, neither good nor bad, bad or very bad. The ratings of very good, good, and neither

good nor bad were grouped together for reporting purposes.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 1 and Week 5    |           |

Notes:

[39] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                 | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|--|---|---|--|--|
| Subject group type                               | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                      | 32  | 8   |  |  |
| Units: Participants                              |   |   |  |  |
| Week 1 Very good, good, and neither good nor bad | 18  | 5   |  |  |
| Week 5 Very good, good, and neither good nor bad | 20  | 6   |  |  |
| Week 1 Bad                                       | 4   | 2   |  |  |
| Week 5 Bad                                       | 1   | 0   |  |  |
| Week 1 Very bad                                  | 0   | 0   |  |  |
| Week 5 Very bad                                  | 1   | 0   |  |  |
| Week 1 Unable to answer question                 | 5   | 0   |  |  |
| Week 5 Unable to answer question                 | 2   | 0   |  |  |
| Week 1 Missing                                   | 5   | 1   |  |  |
| Week 5 Missing                                   | 8   | 2   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG and LGG cohort: Palatability of trametinib oral solution based on the palatability questionnaire item: taste of the medication before rinsing the mouth

|                 |   |
|-----------------|---|
| End point title | HGG and LGG cohort: Palatability of trametinib oral solution based on the palatability questionnaire item: taste of the medication before rinsing the mouth <sup>[40]</sup> |
|-----------------|---|

End point description:

Participants who received the trametinib oral solution completed a questionnaire to evaluate the palatability of the pediatric formulation. After taking the medication, participants provided feedback on how it tasted before rinsing with water, rating their experience as very good, good, neither good nor bad, bad or very bad. The ratings of very good, good, and neither good nor bad were grouped together for reporting purposes.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 1 and Week 5    |           |

Notes:

[40] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                 | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|--|---|---|--|--|
| Subject group type                               | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                      | 35  | 8   |  |  |
| Units: Participants                              |   |   |  |  |
| Week 1 Very good, good, and neither good nor bad | 15  | 2   |  |  |
| Week 5 Very good, good, and neither good nor bad | 12  | 5   |  |  |
| Week 1 Bad                                       | 5   | 3   |  |  |
| Week 5 Bad                                       | 6   | 0   |  |  |
| Week 1 Very bad                                  | 2   | 0   |  |  |
| Week 5 Very bad                                  | 2   | 0   |  |  |
| Week 1 Unable to answer question                 | 4   | 1   |  |  |
| Week 5 Unable to answer question                 | 1   | 0   |  |  |
| Week 1 Missing                                   | 9   | 2   |  |  |
| Week 5 Missing                                   | 14  | 3   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG and LGG cohort: Palatability of dabrafenib oral suspension based on the palatability assessment: after- taste once the medication was swallowed

|                 |   |
|-----------------|---|
| End point title | HGG and LGG cohort: Palatability of dabrafenib oral suspension based on the palatability assessment: after- taste once the medication was swallowed <sup>[41]</sup> |
|-----------------|---|

End point description:

Participants who received the dabrafenib dispersible tablets for oral suspension completed a questionnaire to evaluate the palatability of the pediatric formulation. After taking the medication, participants provided feedback on the after-taste of the medication after the medication was swallowed, rating their experience as very good, good, neither good nor bad, bad or very bad. The ratings of very good, good, and neither good nor bad were grouped together for reporting purposes.

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

End point timeframe:

Week 1 and Week 5

Notes:

[41] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                 | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|--|---|---|--|--|
| Subject group type                               | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                      | 32  | 8   |  |  |
| Units: Participants                              |   |   |  |  |
| Week 1 Very good, good, and neither good nor bad | 13  | 4   |  |  |
| Week 5 Very good, good, and neither good nor bad | 16  | 5   |  |  |
| Week 1 Bad                                       | 6   | 1   |  |  |

|                                  |    |   |  |  |
|----------------------------------|----|---|--|--|
| Week 5 Bad                       | 2  | 0 |  |  |
| Week 1 Very bad                  | 0  | 0 |  |  |
| Week 5 Very bad                  | 0  | 0 |  |  |
| Week 1 Unable to answer question | 3  | 0 |  |  |
| Week 5 Unable to answer question | 3  | 0 |  |  |
| Week 1 Missing                   | 10 | 3 |  |  |
| Week 5 Missing                   | 11 | 3 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG and LGG cohort: Palatability of trametinib oral solution based on the palatability assessment: after- taste once the medication was swallowed

|                 |   |
|-----------------|---|
| End point title | HGG and LGG cohort: Palatability of trametinib oral solution based on the palatability assessment: after- taste once the medication was swallowed <sup>[42]</sup> |
|-----------------|---|

End point description:

Participants who received the trametinib oral solution completed a questionnaire to evaluate the palatability of the pediatric formulation. After taking the medication, participants provided feedback on the after-taste of the medication after the medication was swallowed, rating their experience as very good, good, neither good nor bad, bad or very bad. The ratings of very good, good, and neither good nor bad were grouped together for reporting purposes.

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

End point timeframe:

Week 1 and Week 5

Notes:

[42] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                 | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|--|---|---|--|--|
| Subject group type                               | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                      | 35  | 8   |  |  |
| Units: Participants                              |   |   |  |  |
| Week 1 Very good, good, and neither good nor bad | 15  | 3   |  |  |
| Week 5 Very good, good, and neither good nor bad | 16  | 5   |  |  |
| Week 1 Bad                                       | 5   | 3   |  |  |
| Week 5 Bad                                       | 3   | 0   |  |  |
| Week 1 Very bad                                  | 2   | 0   |  |  |
| Week 5 Very bad                                  | 1   | 0   |  |  |
| Week 1 Unable to answer question                 | 2   | 0   |  |  |
| Week 5 Unable to answer question                 | 2   | 0   |  |  |
| Week 1 Missing                                   | 11  | 2   |  |  |
| Week 5 Missing                                   | 13  | 3   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: HGG and LGG cohort: Palatability of dabrafenib oral suspension based on the palatability questionnaire item: immediate reaction once the medication was placed into the mouth

|                 |   |
|-----------------|---|
| End point title | HGG and LGG cohort: Palatability of dabrafenib oral suspension based on the palatability questionnaire item: immediate reaction once the medication was placed into the mouth <sup>[43]</sup> |
|-----------------|---|

#### End point description:

Participants who received the dabrafenib dispersible tablets for oral suspension completed a questionnaire to evaluate the palatability of the pediatric formulation. After taking the medication, participants provided feedback on the immediate reaction once the medication was placed into their mouth, rating their experience as very good, good, neither good nor bad, bad or very bad. The ratings of very good, good, and neither good nor bad were grouped together for reporting purposes.

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

#### End point timeframe:

Week 1 and Week 5

#### Notes:

[43] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                 | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|--|---|---|--|--|
| Subject group type                               | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                      | 32  | 8   |  |  |
| Units: Participants                              |   |   |  |  |
| Week 1 Very good, good, and neither good nor bad | 13  | 4   |  |  |
| Week 5 Very good, good, and neither good nor bad | 18  | 5   |  |  |
| Week 1 Bad                                       | 5   | 1   |  |  |
| Week 5 Bad                                       | 1   | 0   |  |  |
| Week 1 Very bad                                  | 1   | 0   |  |  |
| Week 5 Very bad                                  | 0   | 0   |  |  |
| Week 1 Unable to answer question                 | 3   | 0   |  |  |
| Week 5 Unable to answer question                 | 2   | 0   |  |  |
| Week 1 Missing                                   | 10  | 3   |  |  |
| Week 5 Missing                                   | 11  | 3   |  |  |

## Statistical analyses

**Secondary: HGG and LGG cohort: Palatability of trametinib oral solution based on the palatability assessment: immediate reaction once the medication was placed into the mouth**

|                 |   |
|-----------------|---|
| End point title | HGG and LGG cohort: Palatability of trametinib oral solution based on the palatability assessment: immediate reaction once the medication was placed into the mouth <sup>[44]</sup> |
|-----------------|---|

## End point description:

Participants who received the trametinib oral solution completed a questionnaire to evaluate the palatability of the pediatric formulation. After taking the medication, participants provided feedback on the immediate reaction once the medication was placed into their mouth, rating their experience as very good, good, neither good nor bad, bad or very bad. The ratings of very good, good, and neither good nor bad were grouped together for reporting purposes.

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

## End point timeframe:

Week 1 and Week 5

## Notes:

[44] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                 | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|--|---|---|--|--|
| Subject group type                               | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                      | 35  | 8   |  |  |
| Units: Participants                              |   |   |  |  |
| Week 1 Very good, good, and neither good nor bad | 15  | 3   |  |  |
| Week 5 Very good, good, and neither good nor bad | 15  | 5   |  |  |
| Week 1 Bad                                       | 4   | 3   |  |  |
| Week 5 Bad                                       | 4   | 0   |  |  |
| Week 1 Very Bad                                  | 3   | 0   |  |  |
| Week 5 Very Bad                                  | 2   | 0   |  |  |
| Week 1 Unable to answer question                 | 2   | 0   |  |  |
| Week 5 Unable to answer question                 | 1   | 0   |  |  |
| Week 1 Missing                                   | 11  | 2   |  |  |
| Week 5 Missing                                   | 13  | 3   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: HGG and LGG cohort: Palatability of dabrafenib oral suspension based on the palatability questionnaire item: remaining after-taste once rinsing the mouth with water**

|                 |  |
|-----------------|--|
| End point title | HGG and LGG cohort: Palatability of dabrafenib oral suspension based on the palatability questionnaire item: remaining after-taste once rinsing the mouth with water <sup>[45]</sup> |
|-----------------|--|

## End point description:

Participants who received the dabrafenib dispersible tablets for oral suspension completed a

questionnaire to evaluate the palatability of the pediatric formulation. After taking the medication, participants provided feedback on the after-taste of the medication after rinsing with water, rating their experience as very good, good, neither good nor bad, bad or very bad. The ratings of very good, good, and neither good nor bad were grouped together for reporting purposes.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 1 and Week 5    |           |

Notes:

[45] - 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: This endpoint is reporting results for all arms receiving dabrafenib

| End point values                                 | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|--|---|---|--|--|
| Subject group type                               | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                      | 32  | 8   |  |  |
| Units: Participants                              |   |   |  |  |
| Week 1 Very good, good, and neither good nor bad | 15  | 4   |  |  |
| Week 5 Very good, good, and neither good nor bad | 17  | 6   |  |  |
| Week 1 Bad                                       | 5   | 2   |  |  |
| Week 5 Bad                                       | 2   | 0   |  |  |
| Week 1 Very bad                                  | 0   | 0   |  |  |
| Week 5 Very bad                                  | 1   | 0   |  |  |
| Week 1 Unable to answer question                 | 7   | 1   |  |  |
| Week 5 Unable to answer question                 | 4   | 0   |  |  |
| Week 1 Missing                                   | 5   | 1   |  |  |
| Week 5 Missing                                   | 8   | 2   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HGG and LGG cohort: Palatability of trametinib oral solution based on the palatability assessment: remaining after-taste once rinsing the mouth with water

|                 |  |
|-----------------|--|
| End point title | HGG and LGG cohort: Palatability of trametinib oral solution based on the palatability assessment: remaining after-taste once rinsing the mouth with water <sup>[46]</sup> |
|-----------------|--|

End point description:

Participants who received the trametinib oral solution completed a questionnaire to evaluate the palatability of the pediatric formulation. After taking the medication, participants provided feedback on the after-taste of the medication after rinsing with water, rating their experience as very good, good, neither good nor bad, bad or very bad. The ratings of very good, good, and neither good nor bad were grouped together for reporting purposes.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 1 and Week 5    |           |

Notes:

[46] - 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: This endpoint is reporting results for all arms receiving trametinib

| End point values                                 | LGG cohort:<br>dabrafenib and<br>trametinib | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |
|--|---|---|--|--|
| Subject group type                               | Reporting group                             | Reporting group                             |  |  |
| Number of subjects analysed                      | 35  | 8   |  |  |
| Units: Participants                              |   |   |  |  |
| Week 1 Very good, good, and neither good nor bad | 15  | 2   |  |  |
| Week 5 Very good, good, and neither good nor bad | 14  | 4   |  |  |
| Week 1 Bad                                       | 3   | 2   |  |  |
| Week 5 Bad                                       | 2   | 0   |  |  |
| Week 1 Very Bad                                  | 2   | 0   |  |  |
| Week 5 Very Bad                                  | 2   | 0   |  |  |
| Week 1 Unable to answer question                 | 6   | 2   |  |  |
| Week 5 Unable to answer question                 | 3   | 1   |  |  |
| Week 1 Missing                                   | 9   | 2   |  |  |
| Week 5 Missing                                   | 14  | 3   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LGG cohort: PROMIS Parent Proxy Global Health 7+2 scores- Global health score

|                 |   |
|-----------------|---|
| End point title | LGG cohort: PROMIS Parent Proxy Global Health 7+2 scores- Global health score <sup>[47]</sup> |
|-----------------|---|

End point description:

The PROMIS Parent Proxy Global Health 7+2 was used to evaluate the quality of life of participants. The questionnaire included 7 items measuring the global health of the patient. 4 of the 7 items used a 5-level Likert scale with 1=poor and 5=excellent; 1 of the 7 items used a 5-level Likert scale with 1=never and 5=always; and 2 of the 7 items used a 5-level Likert scale with 1=never and 5=almost always. Global health scores ranged from 7 to 35, higher scores indicate better overall wellbeing (i.e physical, mental, and social health).

Participants who discontinued treatment for reasons other than disease progression entered the post-treatment efficacy follow-up phase, where the PROMIS Parent Proxy Global 7+2 Health questionnaire was performed every 16 weeks until disease progression, withdrawal of consent by patient or a parental/legal guardian, or lost to follow-up.

9999 indicates that the value was not estimable

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

End point timeframe:

Baseline, and Day 1 of Week 5, 8, 16, 24, 32, 49, 48 and 56, and thereafter every 16 weeks until end of treatment (EOT), EOT, and every 16 weeks in the post-treatment efficacy follow-up phase until disease progression (assessed up to 4.6 years)

Notes:

[47] - 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: This endpoint is reporting results for LGG cohort arms



| End point values                      | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|---------------------------------------|---|---|--|--|
| Subject group type                    | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed           | 61  | 23  |  |  |
| Units: Score on a Scale               |   |   |  |  |
| arithmetic mean (standard deviation)  |   |   |  |  |
| Baseline (n= 61 / 23)                 | 42.67 (± 10.068)                            | 42.89 (± 10.502)                              |  |  |
| Week 5 Day 1 (n= 50 / 18)             | 42.14 (± 9.439)                             | 39.06 (± 10.109)                              |  |  |
| Week 8 Day 1 (n= 53 / 18)             | 43.83 (± 9.461)                             | 38.36 (± 7.759)                               |  |  |
| Week 16 Day 1 (n= 48 / 10)            | 44.68 (± 9.159)                             | 41.11 (± 10.798)                              |  |  |
| Week 24 Day 1 (n= 46 / 10)            | 45.27 (± 9.168)                             | 36.57 (± 6.241)                               |  |  |
| Week 32 Day 1 (n= 47 / 11)            | 45.46 (± 8.887)                             | 40.96 (± 7.159)                               |  |  |
| Week 40 Day 1 (n= 40 / 7)             | 45.37 (± 9.687)                             | 38.84 (± 4.960)                               |  |  |
| Week 48 Day 1 (n= 43 / 10)            | 44.83 (± 9.421)                             | 41.56 (± 6.953)                               |  |  |
| Week 56 Day 1 (n= 46 / 7)             | 44.54 (± 8.876)                             | 38.66 (± 8.851)                               |  |  |
| Week 72 Day 1 (n= 40 / 0)             | 44.21 (± 8.967)                             | 9999 (± 9999)                                 |  |  |
| Week 88 Day 1 (n= 38 / 0)             | 44.91 (± 8.847)                             | 9999 (± 9999)                                 |  |  |
| Week 104 Day 1 (n= 39 / 0)            | 45.60 (± 8.231)                             | 9999 (± 9999)                                 |  |  |
| Week 120 Day 1 (n= 33 / 0)            | 44.41 (± 7.317)                             | 9999 (± 9999)                                 |  |  |
| Week 136 Day 1 (n= 24 / 0)            | 44.45 (± 8.074)                             | 9999 (± 9999)                                 |  |  |
| Week 152 Day 1 (n= 17 / 0)            | 47.88 (± 10.534)                            | 9999 (± 9999)                                 |  |  |
| Week 168 Day 1 (n= 13 / 0)            | 46.48 (± 9.888)                             | 9999 (± 9999)                                 |  |  |
| EOT (n= 50 / 14)                      | 44.98 (± 10.274)                            | 39.69 (± 10.536)                              |  |  |
| Post Treatment Follow-Up 1 (n= 1 / 4) | 45.40 (± 9999)                              | 45.53 (± 6.288)                               |  |  |
| Post Treatment Follow-Up 2 (n= 1 / 1) | 27.70 (± 9999)                              | 39.70 (± 9999)                                |  |  |
| Post Treatment Follow-Up 3 (n= 1 / 1) | 43.60 (± 9999)                              | 34.60 (± 9999)                                |  |  |
| Post Treatment Follow-Up 4 (n= 1 / 2) | 31.20 (± 9999)                              | 43.60 (± 8.061)                               |  |  |
| Post Treatment Follow-Up 5 (n= 1 / 1) | 29.40 (± 9999)                              | 37.90 (± 9999)                                |  |  |
| Post Treatment Follow-Up 6 (n= 0 / 2) | 9999 (± 9999)                               | 36.45 (± 7.425)                               |  |  |
| Post Treatment Follow-Up 7 (n= 0 / 0) | 9999 (± 9999)                               | 9999 (± 9999)                                 |  |  |
| Post Treatment Follow-Up 8 (n= 0 / 1) | 9999 (± 9999)                               | 37.90 (± 9999)                                |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: LGG cohort: PROMIS Parent Proxy Global Health 7+2 scores- Pain score**

|                 |  |
|-----------------|--|
| End point title | LGG cohort: PROMIS Parent Proxy Global Health 7+2 scores- Pain score <sup>[48]</sup> |
|-----------------|--|

## End point description:

The PROMIS Parent Proxy Global Health 7+2 was used to evaluate the quality of life of participants. The questionnaire included 1 item measuring the pain of the participants. Pain item used a 5-level Likert scale with 1= never and 5= almost always, higher scores indicate worsening pain.

Participants who discontinued treatment for reasons other than disease progression entered the post-treatment efficacy follow-up phase, where the PROMIS Parent Proxy Global 7+2 Health questionnaire was performed every 16 weeks until disease progression, withdrawal of consent by patient or a parental/legal guardian, or lost to follow-up.

9999 indicates that the value was not estimable.

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

## End point timeframe:

Baseline, and Day 1 of Week 5, 8, 16, 24, 32, 49, 48 and 56, and thereafter every 16 weeks until end of treatment (EOT), EOT, and every 16 weeks in the post-treatment efficacy follow-up phase until disease progression (assessed up to 4.6 years)

## Notes:

[48] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                     | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|--------------------------------------|---|---|--|--|
| Subject group type                   | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed          | 61  | 23  |  |  |
| Units: Score on a Scale              |   |   |  |  |
| arithmetic mean (standard deviation) |   |   |  |  |
| Baseline (n=61 / 23)                 | 52.14 (± 7.658)                             | 52.64 (± 7.054)                               |  |  |
| Week 5 Day 1 (n=51 / 18)             | 50.11 (± 7.275)                             | 50.97 (± 6.263)                               |  |  |
| Week 8 Day 1 (n=54 / 18)             | 49.93 (± 7.727)                             | 51.00 (± 6.037)                               |  |  |
| Week 16 Day 1 (n=48 / 10)            | 49.72 (± 7.300)                             | 51.75 (± 6.330)                               |  |  |
| Week 24 Day 1 (n=46 / 10)            | 50.65 (± 7.450)                             | 51.81 (± 7.937)                               |  |  |
| Week 32 Day 1 (n=47 / 11)            | 48.77 (± 6.647)                             | 49.59 (± 6.387)                               |  |  |
| Week 40 Day 1 (n=40 / 7)             | 49.87 (± 6.389)                             | 52.52 (± 7.402)                               |  |  |
| Week 48 Day 1 (n=43 / 10)            | 49.89 (± 6.581)                             | 51.20 (± 5.903)                               |  |  |
| Week 56 Day 1 (n=46 / 7)             | 48.14 (± 6.496)                             | 53.99 (± 5.466)                               |  |  |
| Week 72 Day 1 (n=40 / 0)             | 49.46 (± 6.498)                             | 9999 (± 9999)                                 |  |  |
| Week 88 Day 1 (n=38 / 0)             | 47.82 (± 6.083)                             | 9999 (± 9999)                                 |  |  |
| Week 104 Day 1 (n=39 / 0)            | 48.74 (± 6.605)                             | 9999 (± 9999)                                 |  |  |
| Week 120 Day 1 (n=33 / 0)            | 48.56 (± 7.583)                             | 9999 (± 9999)                                 |  |  |
| Week 136 Day 1 (n=24 / 0)            | 46.16 (± 5.305)                             | 9999 (± 9999)                                 |  |  |
| Week 152 Day 1 (n=17 / 0)            | 47.42 (± 6.765)                             | 9999 (± 9999)                                 |  |  |

|                                      |                 |                  |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Week 168 Day 1 (n=13 / 0)            | 48.61 (± 6.298) | 9999 (± 9999)    |  |  |
| EOT (n=50 / 14)                      | 51.46 (± 6.830) | 52.87 (± 6.113)  |  |  |
| Post Treatment Follow-Up 1 (n=1 / 4) | 53.05 (± 9999)  | 50.60 (± 4.900)  |  |  |
| Post Treatment Follow-Up 2 (n=1 / 1) | 58.51 (± 9999)  | 43.25 (± 9999)   |  |  |
| Post Treatment Follow-Up 3 (n=1 / 1) | 53.05 (± 9999)  | 43.25 (± 9999)   |  |  |
| Post Treatment Follow-Up 4 (n=1 / 2) | 58.51 (± 9999)  | 43.25 (± 0.000)  |  |  |
| Post Treatment Follow-Up 5 (n=1 / 1) | 58.51 (± 9999)  | 43.25 (± 9999)   |  |  |
| Post Treatment Follow-Up 6 (n=0 / 2) | 9999 (± 9999)   | 50.88 (± 10.790) |  |  |
| Post Treatment Follow-Up 7 (n=0 / 0) | 9999 (± 9999)   | 9999 (± 9999)    |  |  |
| Post Treatment Follow-Up 8 (n=0 / 1) | 9999 (± 9999)   | 43.25 (± 9999)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: LGG cohort: Parent Proxy Global Health 7+2 scores- Fatigue score

|                 |  |
|-----------------|--|
| End point title | LGG cohort: Parent Proxy Global Health 7+2 scores- Fatigue score <sup>[49]</sup> |
|-----------------|--|

End point description:

The PROMIS Parent Proxy Global Health 7+2 was used to evaluate the quality of life of participants. The questionnaire included 1 item measuring the fatigue interference of the participants. Fatigue item used a 5-level Likert scale with 1= never and 5= almost always, higher scores indicate worsening fatigue. Participants who discontinued treatment for reasons other than disease progression entered the post-treatment efficacy follow-up phase, where the PROMIS Parent Proxy Global 7+2 Health questionnaire was performed every 16 weeks until disease progression, withdrawal of consent by patient or a parental/legal guardian, or lost to follow-up. 9999 indicates that the value was not estimable

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

End point timeframe:

Baseline, and Day 1 of Week 5, 8, 16, 24, 32, 49, 48 and 56, and thereafter every 16 weeks until end of treatment (EOT), EOT, and every 16 weeks in the post-treatment efficacy follow-up phase until disease progression (assessed up to 4.6 years)

Notes:

[49] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                     | LGG cohort: dabrafenib and trametinib | LGG cohort: carboplatin and vincristine |  |  |
|--------------------------------------|---------------------------------------|---|--|--|
| Subject group type                   | Reporting group                       | Reporting group                         |  |  |
| Number of subjects analysed          | 61                                    | 23                                      |  |  |
| Units: Score on a Scale              |                                       |   |  |  |
| arithmetic mean (standard deviation) |                                       |   |  |  |
| Baseline (n= 61 / 23)                | 53.30 (± 6.731)                       | 54.37 (± 7.981)                         |  |  |
| Week 5 Day 1 (n= 51 / 18)            | 53.96 (± 7.588)                       | 56.88 (± 6.430)                         |  |  |
| Week 8 Day 1 (n= 54 / 18)            | 52.68 (± 6.967)                       | 58.10 (± 4.823)                         |  |  |

|                                       |                 |                 |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Week 16 Day 1 (n= 48 / 10)            | 51.22 (± 6.983) | 57.81 (± 6.193) |  |  |
| Week 24 Day 1 (n=46 / 10)             | 51.04 (± 8.005) | 55.02 (± 7.248) |  |  |
| Week 32 Day 1 (n= 47 / 11)            | 52.49 (± 7.219) | 57.66 (± 5.899) |  |  |
| Week 40 Day 1 (n= 40 / 7)             | 52.27 (± 7.450) | 58.49 (± 7.072) |  |  |
| Week 48 Day 1 (n= 43 / 10)            | 51.65 (± 7.362) | 53.48 (± 8.004) |  |  |
| Week 56 Day 1 (n= 46 / 7)             | 50.51 (± 7.150) | 57.63 (± 7.254) |  |  |
| Week 72 Day 1 (n= 40 / 0)             | 49.93 (± 6.910) | 9999 (± 9999)   |  |  |
| Week 88 Day 1 (n= 38 / 0)             | 50.52 (± 7.358) | 9999 (± 9999)   |  |  |
| Week 104 Day 1 (n= 39 / 0)            | 51.11 (± 6.899) | 9999 (± 9999)   |  |  |
| Week 120 Day 1 (n= 33 / 0)            | 50.40 (± 7.317) | 9999 (± 9999)   |  |  |
| Week 136 Day 1 (n= 24 / 0)            | 50.97 (± 8.667) | 9999 (± 9999)   |  |  |
| Week 152 Day 1 (n= 17 / 0)            | 47.71 (± 8.037) | 9999 (± 9999)   |  |  |
| Week 168 Day 1 (n= 13 / 0)            | 48.21 (± 8.188) | 9999 (± 9999)   |  |  |
| EOT (n= 50 / 14)                      | 52.35 (± 7.565) | 56.88 (± 5.246) |  |  |
| Post Treatment Follow-Up 1 (n= 1 / 4) | 48.94 (± 9999)  | 52.36 (± 6.840) |  |  |
| Post Treatment Follow-Up 2 (n= 1 / 1) | 62.62 (± 9999)  | 62.62 (± 9999)  |  |  |
| Post Treatment Follow-Up 3 (n= 1 / 1) | 48.94 (± 9999)  | 48.94 (± 9999)  |  |  |
| Post Treatment Follow-Up 4 (n= 1 / 2) | 56.07 (± 9999)  | 48.94 (± 0.000) |  |  |
| Post Treatment Follow-Up 5 (n= 1 / 1) | 62.62 (± 9999)  | 48.94 (± 9999)  |  |  |
| Post Treatment Follow-Up 6 (n= 0 / 2) | 9999 (± 9999)   | 55.78 (± 9.673) |  |  |
| Post Treatment Follow-Up 7 (n= 0 / 0) | 9999 (± 9999)   | 9999 (± 9999)   |  |  |
| Post Treatment Follow-Up 8 (n= 0 / 1) | 9999 (± 9999)   | 48.94 (± 9999)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: LGG cohort: Overall response rate (ORR) by central independent assessment using RANO criteria (longer follow-up time)

|                 |   |
|-----------------|---|
| End point title | LGG cohort: Overall response rate (ORR) by central independent assessment using RANO criteria (longer follow-up time) <sup>[50]</sup> |
|-----------------|---|

End point description:

Percentage of participants with a best overall confirmed CR or PR as assessed per RANO criteria by central independent assessment. The 95% CIs were computed using two-sided exact binomial method. CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses. PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing

(T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically. This analysis was conducted at the end of the trial (after the primary endpoint analysis cut-off date) and includes a longer follow-up time

|                        |                     |
|------------------------|---------------------|
| End point type         | Other pre-specified |
| End point timeframe:   |                     |
| Up to approx 4.2 years |                     |

Notes:

[50] - 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: This endpoint is reporting results for LGG cohort arms

| End point values                  | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine |  |  |
|-----------------------------------|---|---|--|--|
| Subject group type                | Reporting group                             | Reporting group                               |  |  |
| Number of subjects analysed       | 73  | 37  |  |  |
| Units: Percentage of participants |   |   |  |  |
| number (confidence interval 95%)  | 54.8 (42.7 to<br>66.5)                      | 16.2 (6.2 to<br>32.0)                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: HGG cohort: Overall response rate (ORR) by central independent assessment using RANO criteria (longer follow-up time)

|                 |   |
|-----------------|---|
| End point title | HGG cohort: Overall response rate (ORR) by central independent assessment using RANO criteria (longer follow-up time) <sup>[51]</sup> |
|-----------------|---|

End point description:

Percentage of participants with a best overall confirmed CR or PR as assessed per RANO criteria by central independent assessment. The 95% CIs were computed using two-sided exact binomial method. CR: Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4weeks; no new lesions; and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be off steroids or only on physiologic replacement doses. PR:  $\geq 50\%$  reduction, compared to baseline, in the sum of products of the perpendicular diameters for all measurable lesions for at least 4 weeks, no progression of nonmeasurable disease, no new lesions, and stable or improved nonenhancing (T2/FLAIR) lesions. Patient must be on a corticosteroid dose not greater than the dose at the time of baseline scan and be stable or improving clinically. This analysis was conducted at the end of the trial (after the primary endpoint analysis cut-off date) and includes a longer follow-up time

|                        |                     |
|------------------------|---------------------|
| End point type         | Other pre-specified |
| End point timeframe:   |                     |
| Up to approx 4.8 years |                     |

Notes:

[51] - 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: This endpoint is reporting results for the HGG cohort arm

|                                   |   |  |  |  |
|-----------------------------------|---|--|--|--|
| <b>End point values</b>           | HGG cohort:<br>dabrafenib and<br>trametinib |  |  |  |
| Subject group type                | Reporting group                             |  |  |  |
| Number of subjects analysed       | 41  |  |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (confidence interval 95%)  | 56.1 (39.7 to<br>71.5)                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Post-hoc: All-collected deaths

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

End point description:

On-treatment deaths were collected from 1st dose to 30 days after last dose of treatment (or start of crossover treatment), up to 4.2 years (LGG) and 4.1 years (HGG). Post- treatment efficacy/survival follow-up deaths were collected from 31 days post-treatment to end of study (or start of crossover treatment), up to 4.6 years (LGG) and 5.1 years (HGG). For participants in the LGG cohort who crossed over to dabrafenib and trametinib, on-treatment deaths were collected from 1st dose to 30 days after last dose of crossover treatment, up to 4.2 years. None of the patients who crossed-over were included in the crossover post-treatment efficacy/survival follow-up (FU)

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

End point timeframe:

On-treatment: Up to 4.2 years (LGG) and 4.1 years (HGG). Post- treatment: Up to 4.6 years (LGG) and 5.1 years (HGG).Crossover arm: on-treatment: up to 4.2 years

|  |   |   |   |  |
|--|---|---|---|--|
| <b>End point values</b>                          | LGG cohort:<br>dabrafenib and<br>trametinib | LGG cohort:<br>carboplatin and<br>vincristine | HGG cohort:<br>dabrafenib and<br>trametinib |  |
| Subject group type                               | Reporting group                             | Reporting group                               | Reporting group                             |  |
| Number of subjects analysed                      | 73  | 33  | 41  |  |
| Units: Participants                              |   |   |   |  |
| On- treatment                                    | 0   | 0   | 6   |  |
| Post-treatment efficacy/survival FU              | 0   | 0   | 11  |  |
| Crossover on-treatment                           | 0   | 1   | 0   |  |
| Crossover post-treatment<br>efficacy/survival FU | 0   | 0   | 0   |  |
| All deaths                                       | 0   | 1   | 17  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

On-treatment AEs: from first dose to 30 days after last treatment (or start of crossover treatment), up to 4.2 years (LGG) and 4.1 years (HGG). Crossover on-treatment: AEs from first dose to 30 days after last dose of crossover treatment, up to 4.2 years

Adverse event reporting additional description:

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

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | HGG cohort: dabrafenib + trametinib (On-treatment) |
|-----------------------|--|

Reporting group description:

AEs collected during on-treatment period with dabrafenib and trametinib in the HGG cohort (up to 30 days post- treatment)

|                       |  |
|-----------------------|--|
| Reporting group title | LGG cohort: carboplatin + vincristine (On-treatment) |
|-----------------------|--|

Reporting group description:

AEs collected during on-treatment period with carboplatin and vincristine in the LGG cohort (up to 30 days post- treatment or start date of crossover treatment, whichever was earlier)

|                       |   |
|-----------------------|---|
| Reporting group title | LGG cohort: carboplatin+ vincristine (Crossover On-treatment) |
|-----------------------|---|

Reporting group description:

AEs collected during crossover on-treatment period with dabrafenib and trametinib for participants in the LGG cohort randomized to carboplatin and vincristine who crossed over to dabrafenib and trametinib after disease progression (up to 30 days post- crossover treatment)

|                       |  |
|-----------------------|--|
| Reporting group title | LGG cohort: dabrafenib + trametinib (On-treatment) |
|-----------------------|--|

Reporting group description:

AEs collected during on-treatment period with dabrafenib and trametinib in the LGG cohort (up to 30 days post- treatment)

| Serious adverse events                            | HGG cohort:<br>dabrafenib +<br>trametinib (On-<br>treatment) | LGG cohort:<br>carboplatin +<br>vincristine (On-<br>treatment) | LGG cohort:<br>carboplatin+<br>vincristine<br>(Crossover On-<br>treatment) |
|---|--|--|--|
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 28 / 41 (68.29%)   | 14 / 33 (42.42%)   | 4 / 12 (33.33%)  |
| number of deaths (all causes)                     | 6  | 0  | 1  |
| number of deaths resulting from adverse events    | 0  | 0  | 0  |
| Vascular disorders                                |  |  |  |
| Hypotension                                       |  |  |  |
| subjects affected / exposed                       | 1 / 41 (2.44%)   | 0 / 33 (0.00%)   | 0 / 12 (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  |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| Embolism   |                |                 |                 |
| subjects affected / exposed                          | 0 / 41 (0.00%) | 0 / 33 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                |                 |                 |
| Influenza like illness                               |                |                 |                 |
| subjects affected / exposed                          | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 0 / 12 (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           |
| Pyrexia  |                |                 |                 |
| subjects affected / exposed                          | 3 / 41 (7.32%) | 6 / 33 (18.18%) | 2 / 12 (16.67%) |
| occurrences causally related to treatment / all      | 2 / 3          | 5 / 8           | 2 / 4           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Pain   |                |                 |                 |
| subjects affected / exposed                          | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 0 / 12 (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           |
| Malaise  |                |                 |                 |
| subjects affected / exposed                          | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders             |                |                 |                 |
| Uterine haemorrhage                                  |                |                 |                 |
| subjects affected / exposed                          | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 0 / 12 (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           |
| Respiratory, thoracic and mediastinal disorders      |                |                 |                 |
| Apnoea   |                |                 |                 |
| subjects affected / exposed                          | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0           | 0 / 0           |
| Aspiration   |                |                 |                 |



|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumothorax                                    |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Epistaxis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Atelectasis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Bronchospasm                                    |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tonsillar hypertrophy                           |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders                           |                |                |                |
| Agitation                                       |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Anxiety   |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 1 / 33 (3.03%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Confusional state                               |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Mental status changes                           |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Investigations                                  |                |                |                |
| C-reactive protein increased                    |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Oxygen saturation decreased                     |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Procedural pain                                 |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Procedural complication                         |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Post procedural haemorrhage                     |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Shunt malfunction                               |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |

|  |                                  |                                  |                                  |
|--|----------------------------------|----------------------------------|----------------------------------|
| Tooth avulsion<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                   | 1 / 41 (2.44%)<br>0 / 1<br>0 / 0 | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |
| Fracture<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 41 (2.44%)<br>0 / 1<br>0 / 0 | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |
| Road traffic accident<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                            | 1 / 41 (2.44%)<br>0 / 1<br>0 / 0 | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |
| Nervous system disorders<br>Cerebral haemorrhage<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 41 (2.44%)<br>0 / 1<br>0 / 0 | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |
| Altered state of consciousness<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                   | 1 / 41 (2.44%)<br>0 / 1<br>0 / 0 | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |
| Cerebral ventricle dilatation<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                    | 0 / 41 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |
| Cerebrospinal fluid circulation disorder<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all         | 0 / 41 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 33 (3.03%)<br>0 / 1<br>0 / 0 | 1 / 12 (8.33%)<br>0 / 1<br>0 / 0 |
| Depressed level of consciousness<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | 1 / 41 (2.44%)<br>0 / 1<br>0 / 0 | 0 / 33 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 12 (0.00%)<br>0 / 0<br>0 / 0 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Dizziness                                       |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |
| Dysarthria                                      |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Facial paralysis                                |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Haemorrhage intracranial                        |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |
| Headache  |                |                |                |
| subjects affected / exposed                     | 3 / 41 (7.32%) | 1 / 33 (3.03%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 4          | 1 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hemiparesis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Migraine with aura                              |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |
| Ischaemic cerebral infarction                   |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Intracranial pressure increased                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 41 (4.88%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Hydrocephalus                                   |                |                |                |
| subjects affected / exposed                     | 2 / 41 (4.88%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Paraesthesia                                    |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Paresis   |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Partial seizures                                |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Peripheral motor neuropathy                     |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Peripheral sensory neuropathy                   |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |
| Seizure   |                |                |                |
| subjects affected / exposed                     | 2 / 41 (4.88%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Central nervous system lesion                   |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Optic perineuritis                              |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia   |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Neutropenia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |
| Eye disorders                                   |                |                |                |
| Detachment of retinal pigment epithelium        |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Papilloedema                                    |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Gastrointestinal disorders                      |                |                |                |
| Ascites   |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |
| Constipation                                    |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal haemorrhage                    |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Gastrooesophageal reflux disease                |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (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          |
| Vomiting  |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pancreatitis                                    |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                |                |                |
| Erythema nodosum                                |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Rash  |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Renal and urinary disorders                     |                |                |                |
| Renal colic                                     |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nephrolithiasis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Bacterial sepsis                                |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Encephalomyelitis                               |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 1 / 33 (3.03%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Bronchitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infection                                       |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |



|   |                |                |                |
|---|----------------|----------------|----------------|
| Brain abscess                                   |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Laryngitis                                      |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Toxic shock syndrome                            |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Tooth abscess                                   |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Tonsillitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Varicella                                       |                |                |                |
| subjects affected / exposed                     | 1 / 41 (2.44%) | 0 / 33 (0.00%) | 0 / 12 (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          |
| Urinary tract infection bacterial               |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 41 (0.00%) | 0 / 33 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |                |                |                |

|  |                  |                |                |
|--|------------------|----------------|----------------|
| subjects affected / exposed                              | 0 / 41 (0.00%)   | 1 / 33 (3.03%) | 0 / 12 (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          |
| Viral myositis   |                  |                |                |
| subjects affected / exposed                              | 0 / 41 (0.00%)   | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 0          |
| Haematological infection                                 |                  |                |                |
| subjects affected / exposed                              | 1 / 41 (2.44%)   | 0 / 33 (0.00%) | 0 / 12 (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          |
| Vulvitis   |                  |                |                |
| subjects affected / exposed                              | 0 / 41 (0.00%)   | 0 / 33 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 0          |
| Pneumonia  |                  |                |                |
| subjects affected / exposed                              | 0 / 41 (0.00%)   | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders                       |                  |                |                |
| Dehydration  |                  |                |                |
| subjects affected / exposed                              | 0 / 41 (0.00%)   | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 0          |
| Hypernatraemia   |                  |                |                |
| subjects affected / exposed                              | 0 / 41 (0.00%)   | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all          | 0 / 0            | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all               | 0 / 0            | 0 / 0          | 0 / 0          |
| <b>Serious adverse events</b>                            |                  |                |                |
| LGG cohort:<br>dabrafenib +<br>trametinib (On-treatment) |                  |                |                |
| Total subjects affected by serious adverse events        |                  |                |                |
| subjects affected / exposed                              | 34 / 73 (46.58%) |                |                |
| number of deaths (all causes)                            | 0                |                |                |

|  |                  |  |  |
|--|------------------|--|--|
| number of deaths resulting from adverse events       | 0                |  |  |
| Vascular disorders                                   |                  |  |  |
| Hypotension  |                  |  |  |
| subjects affected / exposed                          | 0 / 73 (0.00%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Embolism   |                  |  |  |
| subjects affected / exposed                          | 1 / 73 (1.37%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| General disorders and administration site conditions |                  |  |  |
| Influenza like illness                               |                  |  |  |
| subjects affected / exposed                          | 0 / 73 (0.00%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Pyrexia  |                  |  |  |
| subjects affected / exposed                          | 12 / 73 (16.44%) |  |  |
| occurrences causally related to treatment / all      | 22 / 29          |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Pain   |                  |  |  |
| subjects affected / exposed                          | 0 / 73 (0.00%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Malaise  |                  |  |  |
| subjects affected / exposed                          | 0 / 73 (0.00%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Reproductive system and breast disorders             |                  |  |  |
| Uterine haemorrhage                                  |                  |  |  |
| subjects affected / exposed                          | 0 / 73 (0.00%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 0            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Respiratory, thoracic and mediastinal disorders      |                  |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Apnoea  |                |  |  |  |
| subjects affected / exposed                     | 2 / 73 (2.74%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Aspiration                                      |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumothorax                                    |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Epistaxis                                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Atelectasis                                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Bronchospasm                                    |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Tonsillar hypertrophy                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Psychiatric disorders                           |                |  |  |  |
| Agitation                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Anxiety   |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Confusional state                               |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Mental status changes                           |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| C-reactive protein increased                    |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Oxygen saturation decreased                     |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Procedural pain                                 |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Procedural complication                         |                |  |  |
| subjects affected / exposed                     | 2 / 73 (2.74%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Post procedural haemorrhage                     |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Shunt malfunction                               |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Tooth avulsion                                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Fracture  |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Road traffic accident                           |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Nervous system disorders                        |                |  |  |  |
| Cerebral haemorrhage                            |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Altered state of consciousness                  |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cerebral ventricle dilatation                   |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cerebrospinal fluid circulation disorder        |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Depressed level of consciousness<br>subjects affected / exposed | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |  |
| Dizziness<br>subjects affected / exposed                        | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |  |
| Dysarthria<br>subjects affected / exposed                       | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |  |
| Facial paralysis<br>subjects affected / exposed                 | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |  |
| Haemorrhage intracranial<br>subjects affected / exposed         | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |  |
| Headache<br>subjects affected / exposed                         | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 1          |  |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |  |
| Hemiparesis<br>subjects affected / exposed                      | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |  |
| Migraine with aura<br>subjects affected / exposed               | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          |  |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          |  |  |  |
| Ischaemic cerebral infarction                                   |                |  |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Intracranial pressure increased                 |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Hydrocephalus                                   |                |  |  |  |
| subjects affected / exposed                     | 2 / 73 (2.74%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Paraesthesia                                    |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Paresis   |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Partial seizures                                |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Peripheral motor neuropathy                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Peripheral sensory neuropathy                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Seizure   |                |  |  |  |



|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 2 / 73 (2.74%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Central nervous system lesion                   |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Optic perineuritis                              |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Syncope   |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Anaemia   |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Febrile neutropenia                             |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Neutropenia                                     |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Detachment of retinal pigment epithelium        |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Papilloedema                                    |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Ascites   |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal haemorrhage                    |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrooesophageal reflux disease                |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 3 / 73 (4.11%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper gastrointestinal haemorrhage              |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pancreatitis                                    |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Erythema nodosum                                |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Rash  |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Renal colic                                     |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nephrolithiasis                                 |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Bacterial sepsis                                |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Encephalomyelitis                               |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Device related infection                        |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bronchitis                                      |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| Infection                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Brain abscess                                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Laryngitis                                      |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Toxic shock syndrome                            |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Tooth abscess                                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Tonsillitis                                     |                |  |  |  |
| subjects affected / exposed                     | 3 / 73 (4.11%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Varicella                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Urinary tract infection bacterial               |                |  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Urinary tract infection                         |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 2 / 73 (2.74%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper respiratory tract infection               |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Viral myositis                                  |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haematological infection                        |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vulvitis  |                |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypernatraemia                                  |                |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>  | HGG cohort:<br>dabrafenib +<br>trametinib (On-<br>treatment) | LGG cohort:<br>carboplatin +<br>vincristine (On-<br>treatment) | LGG cohort:<br>carboplatin+<br>vincristine<br>(Crossover On-<br>treatment) |
|--|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 41 / 41 (100.00%)  | 33 / 33 (100.00%)  | 11 / 12 (91.67%)   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                  |  |  |  |
| Skin papilloma   |  |  |  |
| subjects affected / exposed  | 4 / 41 (9.76%)   | 0 / 33 (0.00%)   | 1 / 12 (8.33%)   |
| occurrences (all)  | 6  | 0  | 1  |
| Melanocytic naevus   |  |  |  |
| subjects affected / exposed  | 2 / 41 (4.88%)   | 0 / 33 (0.00%)   | 2 / 12 (16.67%)  |
| occurrences (all)  | 3  | 0  | 2  |
| General disorders and administration site conditions                                 |  |  |  |
| Asthenia   |  |  |  |
| subjects affected / exposed  | 2 / 41 (4.88%)   | 3 / 33 (9.09%)   | 1 / 12 (8.33%)   |
| occurrences (all)  | 3  | 5  | 1  |
| Catheter site pain   |  |  |  |
| subjects affected / exposed  | 0 / 41 (0.00%)   | 2 / 33 (6.06%)   | 0 / 12 (0.00%)   |
| occurrences (all)  | 0  | 3  | 0  |
| Chills   |  |  |  |
| subjects affected / exposed  | 1 / 41 (2.44%)   | 1 / 33 (3.03%)   | 0 / 12 (0.00%)   |
| occurrences (all)  | 2  | 1  | 0  |
| Facial pain  |  |  |  |
| subjects affected / exposed  | 0 / 41 (0.00%)   | 3 / 33 (9.09%)   | 0 / 12 (0.00%)   |
| occurrences (all)  | 0  | 5  | 0  |
| Influenza like illness   |  |  |  |
| subjects affected / exposed  | 1 / 41 (2.44%)   | 2 / 33 (6.06%)   | 0 / 12 (0.00%)   |
| occurrences (all)  | 1  | 2  | 0  |
| Fatigue  |  |  |  |
| subjects affected / exposed  | 6 / 41 (14.63%)  | 10 / 33 (30.30%)   | 1 / 12 (8.33%)   |
| occurrences (all)  | 7  | 16   | 2  |
| Oedema peripheral  |  |  |  |

|   |                  |                 |                 |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed                     | 4 / 41 (9.76%)   | 0 / 33 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)                               | 7                | 0               | 0               |
| Pyrexia   |                  |                 |                 |
| subjects affected / exposed                     | 20 / 41 (48.78%) | 2 / 33 (6.06%)  | 7 / 12 (58.33%) |
| occurrences (all)                               | 81               | 4               | 50              |
| Malaise   |                  |                 |                 |
| subjects affected / exposed                     | 1 / 41 (2.44%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                               | 1                | 0               | 1               |
| Cyst  |                  |                 |                 |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                               | 0                | 0               | 1               |
| Gait disturbance                                |                  |                 |                 |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 1 / 33 (3.03%)  | 1 / 12 (8.33%)  |
| occurrences (all)                               | 0                | 1               | 1               |
| Hyperpyrexia                                    |                  |                 |                 |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                               | 0                | 0               | 1               |
| Non-cardiac chest pain                          |                  |                 |                 |
| subjects affected / exposed                     | 2 / 41 (4.88%)   | 2 / 33 (6.06%)  | 2 / 12 (16.67%) |
| occurrences (all)                               | 3                | 3               | 3               |
| Immune system disorders                         |                  |                 |                 |
| Hypersensitivity                                |                  |                 |                 |
| subjects affected / exposed                     | 1 / 41 (2.44%)   | 6 / 33 (18.18%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 1                | 8               | 0               |
| Reproductive system and breast disorders        |                  |                 |                 |
| Pelvic pain                                     |                  |                 |                 |
| subjects affected / exposed                     | 0 / 41 (0.00%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                               | 0                | 0               | 1               |
| Respiratory, thoracic and mediastinal disorders |                  |                 |                 |
| Nasal congestion                                |                  |                 |                 |
| subjects affected / exposed                     | 4 / 41 (9.76%)   | 2 / 33 (6.06%)  | 2 / 12 (16.67%) |
| occurrences (all)                               | 4                | 3               | 2               |
| Cough   |                  |                 |                 |
| subjects affected / exposed                     | 7 / 41 (17.07%)  | 4 / 33 (12.12%) | 3 / 12 (25.00%) |
| occurrences (all)                               | 9                | 7               | 6               |
| Dysphonia                                       |                  |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 41 (0.00%)  | 2 / 33 (6.06%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0               |
| Epistaxis                   |                 |                 |                 |
| subjects affected / exposed | 6 / 41 (14.63%) | 1 / 33 (3.03%)  | 2 / 12 (16.67%) |
| occurrences (all)           | 7               | 2               | 2               |
| Oropharyngeal pain          |                 |                 |                 |
| subjects affected / exposed | 6 / 41 (14.63%) | 7 / 33 (21.21%) | 4 / 12 (33.33%) |
| occurrences (all)           | 6               | 8               | 5               |
| Rhinitis allergic           |                 |                 |                 |
| subjects affected / exposed | 0 / 41 (0.00%)  | 2 / 33 (6.06%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0               |
| Rhinorrhoea                 |                 |                 |                 |
| subjects affected / exposed | 1 / 41 (2.44%)  | 4 / 33 (12.12%) | 2 / 12 (16.67%) |
| occurrences (all)           | 1               | 4               | 3               |
| Tonsillar hypertrophy       |                 |                 |                 |
| subjects affected / exposed | 1 / 41 (2.44%)  | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 1               | 0               | 1               |
| Dyspnoea                    |                 |                 |                 |
| subjects affected / exposed | 2 / 41 (4.88%)  | 2 / 33 (6.06%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 3               | 2               | 1               |
| Snoring                     |                 |                 |                 |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Psychiatric disorders       |                 |                 |                 |
| Anxiety                     |                 |                 |                 |
| subjects affected / exposed | 2 / 41 (4.88%)  | 5 / 33 (15.15%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 2               | 6               | 0               |
| Intentional self-injury     |                 |                 |                 |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Insomnia                    |                 |                 |                 |
| subjects affected / exposed | 3 / 41 (7.32%)  | 1 / 33 (3.03%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 4               | 1               | 0               |
| Mental status changes       |                 |                 |                 |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 0               | 0               | 1               |



|  |                      |                        |                      |
|--|----------------------|------------------------|----------------------|
| Somatic symptom disorder<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 41 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0    | 1 / 12 (8.33%)<br>1  |
| Product issues<br>Device malfunction<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 41 (2.44%)<br>1  | 0 / 33 (0.00%)<br>0    | 1 / 12 (8.33%)<br>1  |
| Investigations<br>Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 41 (7.32%)<br>3  | 5 / 33 (15.15%)<br>15  | 3 / 12 (25.00%)<br>4 |
| Blood bicarbonate decreased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 41 (0.00%)<br>0  | 3 / 33 (9.09%)<br>9    | 0 / 12 (0.00%)<br>0  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 41 (7.32%)<br>4  | 1 / 33 (3.03%)<br>1    | 0 / 12 (0.00%)<br>0  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                     | 4 / 41 (9.76%)<br>5  | 9 / 33 (27.27%)<br>18  | 2 / 12 (16.67%)<br>3 |
| Ejection fraction decreased<br>subjects affected / exposed<br>occurrences (all)                            | 4 / 41 (9.76%)<br>4  | 0 / 33 (0.00%)<br>0    | 0 / 12 (0.00%)<br>0  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                             | 3 / 41 (7.32%)<br>4  | 5 / 33 (15.15%)<br>16  | 0 / 12 (0.00%)<br>0  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 41 (4.88%)<br>13 | 16 / 33 (48.48%)<br>43 | 2 / 12 (16.67%)<br>2 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 41 (2.44%)<br>1  | 10 / 33 (30.30%)<br>29 | 0 / 12 (0.00%)<br>0  |
| SARS-CoV-2 test negative<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 41 (4.88%)<br>2  | 1 / 33 (3.03%)<br>1    | 2 / 12 (16.67%)<br>3 |
| Weight increased   |                      |                        |                      |

|  |                 |                  |                |
|--|-----------------|------------------|----------------|
| subjects affected / exposed                    | 6 / 41 (14.63%) | 0 / 33 (0.00%)   | 0 / 12 (0.00%) |
| occurrences (all)                              | 6               | 0                | 0              |
| Weight decreased                               |                 |                  |                |
| subjects affected / exposed                    | 1 / 41 (2.44%)  | 4 / 33 (12.12%)  | 0 / 12 (0.00%) |
| occurrences (all)                              | 1               | 4                | 0              |
| White blood cell count decreased               |                 |                  |                |
| subjects affected / exposed                    | 5 / 41 (12.20%) | 12 / 33 (36.36%) | 1 / 12 (8.33%) |
| occurrences (all)                              | 8               | 43               | 1              |
| Streptococcus test positive                    |                 |                  |                |
| subjects affected / exposed                    | 0 / 41 (0.00%)  | 0 / 33 (0.00%)   | 1 / 12 (8.33%) |
| occurrences (all)                              | 0               | 0                | 1              |
| Blood pressure decreased                       |                 |                  |                |
| subjects affected / exposed                    | 0 / 41 (0.00%)  | 0 / 33 (0.00%)   | 1 / 12 (8.33%) |
| occurrences (all)                              | 0               | 0                | 1              |
| SARS-CoV-2 test positive                       |                 |                  |                |
| subjects affected / exposed                    | 0 / 41 (0.00%)  | 1 / 33 (3.03%)   | 0 / 12 (0.00%) |
| occurrences (all)                              | 0               | 1                | 0              |
| Injury, poisoning and procedural complications |                 |                  |                |
| Contusion                                      |                 |                  |                |
| subjects affected / exposed                    | 2 / 41 (4.88%)  | 3 / 33 (9.09%)   | 0 / 12 (0.00%) |
| occurrences (all)                              | 3               | 3                | 0              |
| Procedural pain                                |                 |                  |                |
| subjects affected / exposed                    | 0 / 41 (0.00%)  | 2 / 33 (6.06%)   | 0 / 12 (0.00%) |
| occurrences (all)                              | 0               | 2                | 0              |
| Infusion related reaction                      |                 |                  |                |
| subjects affected / exposed                    | 0 / 41 (0.00%)  | 5 / 33 (15.15%)  | 0 / 12 (0.00%) |
| occurrences (all)                              | 0               | 8                | 0              |
| Head injury                                    |                 |                  |                |
| subjects affected / exposed                    | 3 / 41 (7.32%)  | 0 / 33 (0.00%)   | 0 / 12 (0.00%) |
| occurrences (all)                              | 3               | 0                | 0              |
| Arthropod bite                                 |                 |                  |                |
| subjects affected / exposed                    | 3 / 41 (7.32%)  | 0 / 33 (0.00%)   | 0 / 12 (0.00%) |
| occurrences (all)                              | 5               | 0                | 0              |
| Ligament sprain                                |                 |                  |                |

|                               |                  |                 |                 |
|-------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed   | 2 / 41 (4.88%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)             | 2                | 0               | 1               |
| Skin abrasion                 |                  |                 |                 |
| subjects affected / exposed   | 0 / 41 (0.00%)   | 1 / 33 (3.03%)  | 1 / 12 (8.33%)  |
| occurrences (all)             | 0                | 1               | 3               |
| Tibia fracture                |                  |                 |                 |
| subjects affected / exposed   | 0 / 41 (0.00%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)             | 0                | 0               | 1               |
| Cardiac disorders             |                  |                 |                 |
| Aortic valve incompetence     |                  |                 |                 |
| subjects affected / exposed   | 0 / 41 (0.00%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)             | 0                | 0               | 1               |
| Nervous system disorders      |                  |                 |                 |
| Headache                      |                  |                 |                 |
| subjects affected / exposed   | 17 / 41 (41.46%) | 8 / 33 (24.24%) | 7 / 12 (58.33%) |
| occurrences (all)             | 62               | 14              | 10              |
| Dizziness                     |                  |                 |                 |
| subjects affected / exposed   | 4 / 41 (9.76%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)             | 4                | 0               | 1               |
| Neuralgia                     |                  |                 |                 |
| subjects affected / exposed   | 0 / 41 (0.00%)   | 3 / 33 (9.09%)  | 0 / 12 (0.00%)  |
| occurrences (all)             | 0                | 3               | 0               |
| Paraesthesia                  |                  |                 |                 |
| subjects affected / exposed   | 3 / 41 (7.32%)   | 3 / 33 (9.09%)  | 0 / 12 (0.00%)  |
| occurrences (all)             | 3                | 3               | 0               |
| Peripheral motor neuropathy   |                  |                 |                 |
| subjects affected / exposed   | 0 / 41 (0.00%)   | 5 / 33 (15.15%) | 0 / 12 (0.00%)  |
| occurrences (all)             | 0                | 5               | 0               |
| Peripheral sensory neuropathy |                  |                 |                 |
| subjects affected / exposed   | 0 / 41 (0.00%)   | 5 / 33 (15.15%) | 0 / 12 (0.00%)  |
| occurrences (all)             | 0                | 5               | 0               |
| Seizure                       |                  |                 |                 |
| subjects affected / exposed   | 5 / 41 (12.20%)  | 2 / 33 (6.06%)  | 1 / 12 (8.33%)  |
| occurrences (all)             | 11               | 12              | 1               |
| Neuropathy peripheral         |                  |                 |                 |

|   |                      |                        |                      |
|---|----------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                            | 0 / 41 (0.00%)<br>0  | 2 / 33 (6.06%)<br>2    | 0 / 12 (0.00%)<br>0  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)              | 0 / 41 (0.00%)<br>0  | 1 / 33 (3.03%)<br>1    | 2 / 12 (16.67%)<br>2 |
| Ataxia<br>subjects affected / exposed<br>occurrences (all)                  | 3 / 41 (7.32%)<br>3  | 0 / 33 (0.00%)<br>0    | 0 / 12 (0.00%)<br>0  |
| Blood and lymphatic system disorders  |                      |                        |                      |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                 | 4 / 41 (9.76%)<br>6  | 20 / 33 (60.61%)<br>56 | 0 / 12 (0.00%)<br>0  |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)             | 3 / 41 (7.32%)<br>3  | 0 / 33 (0.00%)<br>0    | 0 / 12 (0.00%)<br>0  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)              | 3 / 41 (7.32%)<br>4  | 2 / 33 (6.06%)<br>8    | 0 / 12 (0.00%)<br>0  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)             | 7 / 41 (17.07%)<br>8 | 10 / 33 (30.30%)<br>29 | 1 / 12 (8.33%)<br>1  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 41 (2.44%)<br>1  | 5 / 33 (15.15%)<br>17  | 0 / 12 (0.00%)<br>0  |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 41 (0.00%)<br>0  | 0 / 33 (0.00%)<br>0    | 1 / 12 (8.33%)<br>1  |
| Ear and labyrinth disorders   |                      |                        |                      |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 41 (2.44%)<br>1  | 2 / 33 (6.06%)<br>2    | 0 / 12 (0.00%)<br>0  |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)                | 1 / 41 (2.44%)<br>1  | 1 / 33 (3.03%)<br>1    | 1 / 12 (8.33%)<br>1  |
| Eye disorders   |                      |                        |                      |

|                             |                  |                 |                 |
|-----------------------------|------------------|-----------------|-----------------|
| Eyelid ptosis               |                  |                 |                 |
| subjects affected / exposed | 0 / 41 (0.00%)   | 2 / 33 (6.06%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0                | 2               | 0               |
| Uveitis                     |                  |                 |                 |
| subjects affected / exposed | 1 / 41 (2.44%)   | 0 / 33 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 1                | 0               | 0               |
| Dry eye                     |                  |                 |                 |
| subjects affected / exposed | 2 / 41 (4.88%)   | 1 / 33 (3.03%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 4                | 1               | 0               |
| Eye pain                    |                  |                 |                 |
| subjects affected / exposed | 1 / 41 (2.44%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 1                | 0               | 2               |
| Vision blurred              |                  |                 |                 |
| subjects affected / exposed | 1 / 41 (2.44%)   | 1 / 33 (3.03%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 1                | 1               | 1               |
| Gastrointestinal disorders  |                  |                 |                 |
| Abdominal pain              |                  |                 |                 |
| subjects affected / exposed | 5 / 41 (12.20%)  | 7 / 33 (21.21%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 10               | 13              | 0               |
| Abdominal pain upper        |                  |                 |                 |
| subjects affected / exposed | 2 / 41 (4.88%)   | 2 / 33 (6.06%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 2                | 3               | 0               |
| Angular cheilitis           |                  |                 |                 |
| subjects affected / exposed | 3 / 41 (7.32%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 4                | 0               | 1               |
| Aphthous ulcer              |                  |                 |                 |
| subjects affected / exposed | 1 / 41 (2.44%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 1                | 0               | 1               |
| Dental caries               |                  |                 |                 |
| subjects affected / exposed | 1 / 41 (2.44%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 1                | 0               | 2               |
| Diarrhoea                   |                  |                 |                 |
| subjects affected / exposed | 10 / 41 (24.39%) | 6 / 33 (18.18%) | 2 / 12 (16.67%) |
| occurrences (all)           | 12               | 7               | 2               |
| Nausea                      |                  |                 |                 |

|  |                  |                  |                 |
|--|------------------|------------------|-----------------|
| subjects affected / exposed            | 11 / 41 (26.83%) | 17 / 33 (51.52%) | 3 / 12 (25.00%) |
| occurrences (all)                      | 17               | 33               | 3               |
| Constipation                           |                  |                  |                 |
| subjects affected / exposed            | 6 / 41 (14.63%)  | 12 / 33 (36.36%) | 1 / 12 (8.33%)  |
| occurrences (all)                      | 9                | 14               | 1               |
| Vomiting                               |                  |                  |                 |
| subjects affected / exposed            | 12 / 41 (29.27%) | 17 / 33 (51.52%) | 6 / 12 (50.00%) |
| occurrences (all)                      | 23               | 61               | 10              |
| Stomatitis                             |                  |                  |                 |
| subjects affected / exposed            | 3 / 41 (7.32%)   | 5 / 33 (15.15%)  | 1 / 12 (8.33%)  |
| occurrences (all)                      | 3                | 7                | 1               |
| Dyspepsia                              |                  |                  |                 |
| subjects affected / exposed            | 0 / 41 (0.00%)   | 2 / 33 (6.06%)   | 0 / 12 (0.00%)  |
| occurrences (all)                      | 0                | 2                | 0               |
| Food poisoning                         |                  |                  |                 |
| subjects affected / exposed            | 0 / 41 (0.00%)   | 0 / 33 (0.00%)   | 1 / 12 (8.33%)  |
| occurrences (all)                      | 0                | 0                | 1               |
| Toothache                              |                  |                  |                 |
| subjects affected / exposed            | 2 / 41 (4.88%)   | 0 / 33 (0.00%)   | 1 / 12 (8.33%)  |
| occurrences (all)                      | 2                | 0                | 1               |
| Skin and subcutaneous tissue disorders |                  |                  |                 |
| Dermatitis acneiform                   |                  |                  |                 |
| subjects affected / exposed            | 4 / 41 (9.76%)   | 0 / 33 (0.00%)   | 2 / 12 (16.67%) |
| occurrences (all)                      | 5                | 0                | 2               |
| Alopecia                               |                  |                  |                 |
| subjects affected / exposed            | 1 / 41 (2.44%)   | 9 / 33 (27.27%)  | 1 / 12 (8.33%)  |
| occurrences (all)                      | 1                | 9                | 1               |
| Dermatitis                             |                  |                  |                 |
| subjects affected / exposed            | 3 / 41 (7.32%)   | 0 / 33 (0.00%)   | 0 / 12 (0.00%)  |
| occurrences (all)                      | 3                | 0                | 0               |
| Acne                                   |                  |                  |                 |
| subjects affected / exposed            | 6 / 41 (14.63%)  | 0 / 33 (0.00%)   | 1 / 12 (8.33%)  |
| occurrences (all)                      | 9                | 0                | 1               |
| Dry skin                               |                  |                  |                 |
| subjects affected / exposed            | 14 / 41 (34.15%) | 1 / 33 (3.03%)   | 1 / 12 (8.33%)  |
| occurrences (all)                      | 17               | 1                | 1               |

|                             |                 |                |                 |
|-----------------------------|-----------------|----------------|-----------------|
| Eczema                      |                 |                |                 |
| subjects affected / exposed | 5 / 41 (12.20%) | 0 / 33 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 9               | 0              | 1               |
| Erythema                    |                 |                |                 |
| subjects affected / exposed | 5 / 41 (12.20%) | 0 / 33 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 6               | 0              | 2               |
| Keratosis pilaris           |                 |                |                 |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 0               | 0              | 1               |
| Hand dermatitis             |                 |                |                 |
| subjects affected / exposed | 1 / 41 (2.44%)  | 0 / 33 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 1               | 0              | 2               |
| Ingrowing nail              |                 |                |                 |
| subjects affected / exposed | 3 / 41 (7.32%)  | 0 / 33 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 3               | 0              | 1               |
| Erythema nodosum            |                 |                |                 |
| subjects affected / exposed | 3 / 41 (7.32%)  | 0 / 33 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 9               | 0              | 0               |
| Panniculitis                |                 |                |                 |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 0               | 0              | 0               |
| Papule                      |                 |                |                 |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all)           | 0               | 0              | 2               |
| Pruritus                    |                 |                |                 |
| subjects affected / exposed | 4 / 41 (9.76%)  | 2 / 33 (6.06%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 5               | 2              | 1               |
| Urticaria                   |                 |                |                 |
| subjects affected / exposed | 5 / 41 (12.20%) | 2 / 33 (6.06%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 5               | 2              | 0               |
| Rash maculo-papular         |                 |                |                 |
| subjects affected / exposed | 6 / 41 (14.63%) | 0 / 33 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 11              | 0              | 2               |
| Skin hyperpigmentation      |                 |                |                 |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)           | 0               | 0              | 1               |

|                             |                 |                |                |
|-----------------------------|-----------------|----------------|----------------|
| Skin striae                 |                 |                |                |
| subjects affected / exposed | 1 / 41 (2.44%)  | 0 / 33 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)           | 1               | 0              | 1              |
| Rash                        |                 |                |                |
| subjects affected / exposed | 9 / 41 (21.95%) | 3 / 33 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all)           | 21              | 4              | 1              |
| Dermatitis contact          |                 |                |                |
| subjects affected / exposed | 3 / 41 (7.32%)  | 0 / 33 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)           | 3               | 0              | 2              |
| Dyshidrotic eczema          |                 |                |                |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)           | 0               | 0              | 1              |
| Rash papular                |                 |                |                |
| subjects affected / exposed | 0 / 41 (0.00%)  | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0               | 0              | 0              |
| Hyperkeratosis              |                 |                |                |
| subjects affected / exposed | 0 / 41 (0.00%)  | 1 / 33 (3.03%) | 1 / 12 (8.33%) |
| occurrences (all)           | 0               | 1              | 1              |
| Rash erythematous           |                 |                |                |
| subjects affected / exposed | 2 / 41 (4.88%)  | 0 / 33 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 2               | 0              | 0              |
| Erythema multiforme         |                 |                |                |
| subjects affected / exposed | 2 / 41 (4.88%)  | 2 / 33 (6.06%) | 0 / 12 (0.00%) |
| occurrences (all)           | 2               | 2              | 0              |
| Skin lesion                 |                 |                |                |
| subjects affected / exposed | 2 / 41 (4.88%)  | 0 / 33 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)           | 5               | 0              | 1              |
| Renal and urinary disorders |                 |                |                |
| Haematuria                  |                 |                |                |
| subjects affected / exposed | 3 / 41 (7.32%)  | 2 / 33 (6.06%) | 1 / 12 (8.33%) |
| occurrences (all)           | 3               | 5              | 2              |
| Proteinuria                 |                 |                |                |
| subjects affected / exposed | 1 / 41 (2.44%)  | 2 / 33 (6.06%) | 0 / 12 (0.00%) |
| occurrences (all)           | 4               | 2              | 0              |
| Endocrine disorders         |                 |                |                |



|   |                     |                      |                      |
|---|---------------------|----------------------|----------------------|
| Growth hormone deficiency<br>subjects affected / exposed<br>occurrences (all) | 1 / 41 (2.44%)<br>1 | 0 / 33 (0.00%)<br>0  | 2 / 12 (16.67%)<br>2 |
| Thyroid disorder<br>subjects affected / exposed<br>occurrences (all)          | 0 / 41 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |
| Musculoskeletal and connective tissue disorders                               |                     |                      |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                | 3 / 41 (7.32%)<br>3 | 1 / 33 (3.03%)<br>1  | 2 / 12 (16.67%)<br>2 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 41 (7.32%)<br>5 | 4 / 33 (12.12%)<br>4 | 0 / 12 (0.00%)<br>0  |
| Muscular weakness<br>subjects affected / exposed<br>occurrences (all)         | 0 / 41 (0.00%)<br>0 | 2 / 33 (6.06%)<br>3  | 0 / 12 (0.00%)<br>0  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 41 (7.32%)<br>5 | 3 / 33 (9.09%)<br>4  | 0 / 12 (0.00%)<br>0  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)         | 4 / 41 (9.76%)<br>4 | 4 / 33 (12.12%)<br>4 | 1 / 12 (8.33%)<br>2  |
| Pain in jaw<br>subjects affected / exposed<br>occurrences (all)               | 0 / 41 (0.00%)<br>0 | 6 / 33 (18.18%)<br>8 | 0 / 12 (0.00%)<br>0  |
| Immobilisation syndrome<br>subjects affected / exposed<br>occurrences (all)   | 0 / 41 (0.00%)<br>0 | 0 / 33 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |
| Infections and infestations   |                     |                      |                      |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)            | 4 / 41 (9.76%)<br>4 | 2 / 33 (6.06%)<br>2  | 0 / 12 (0.00%)<br>0  |
| Gingivitis<br>subjects affected / exposed<br>occurrences (all)                | 1 / 41 (2.44%)<br>1 | 0 / 33 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |
| Nasopharyngitis   |                     |                      |                      |

|                                   |                  |                 |                 |
|-----------------------------------|------------------|-----------------|-----------------|
| subjects affected / exposed       | 2 / 41 (4.88%)   | 2 / 33 (6.06%)  | 1 / 12 (8.33%)  |
| occurrences (all)                 | 2                | 2               | 1               |
| COVID-19                          |                  |                 |                 |
| subjects affected / exposed       | 6 / 41 (14.63%)  | 0 / 33 (0.00%)  | 3 / 12 (25.00%) |
| occurrences (all)                 | 7                | 0               | 4               |
| Urinary tract infection           |                  |                 |                 |
| subjects affected / exposed       | 3 / 41 (7.32%)   | 2 / 33 (6.06%)  | 1 / 12 (8.33%)  |
| occurrences (all)                 | 4                | 2               | 2               |
| Upper respiratory tract infection |                  |                 |                 |
| subjects affected / exposed       | 10 / 41 (24.39%) | 1 / 33 (3.03%)  | 1 / 12 (8.33%)  |
| occurrences (all)                 | 13               | 2               | 2               |
| Rash pustular                     |                  |                 |                 |
| subjects affected / exposed       | 1 / 41 (2.44%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                 | 1                | 0               | 1               |
| Rhinitis                          |                  |                 |                 |
| subjects affected / exposed       | 4 / 41 (9.76%)   | 4 / 33 (12.12%) | 2 / 12 (16.67%) |
| occurrences (all)                 | 5                | 4               | 3               |
| Sinusitis                         |                  |                 |                 |
| subjects affected / exposed       | 2 / 41 (4.88%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                 | 2                | 0               | 1               |
| Paronychia                        |                  |                 |                 |
| subjects affected / exposed       | 3 / 41 (7.32%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                 | 3                | 0               | 2               |
| Otitis media                      |                  |                 |                 |
| subjects affected / exposed       | 1 / 41 (2.44%)   | 2 / 33 (6.06%)  | 0 / 12 (0.00%)  |
| occurrences (all)                 | 1                | 2               | 0               |
| Bronchitis                        |                  |                 |                 |
| subjects affected / exposed       | 0 / 41 (0.00%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                 | 0                | 0               | 1               |
| Ear infection                     |                  |                 |                 |
| subjects affected / exposed       | 0 / 41 (0.00%)   | 0 / 33 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)                 | 0                | 0               | 0               |
| Oral candidiasis                  |                  |                 |                 |
| subjects affected / exposed       | 1 / 41 (2.44%)   | 0 / 33 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)                 | 1                | 0               | 1               |
| Fungal skin infection             |                  |                 |                 |

|                                    |                |                 |                |
|------------------------------------|----------------|-----------------|----------------|
| subjects affected / exposed        | 0 / 41 (0.00%) | 0 / 33 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                  | 0              | 0               | 0              |
| Gastroenteritis                    |                |                 |                |
| subjects affected / exposed        | 2 / 41 (4.88%) | 0 / 33 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                  | 2              | 0               | 1              |
| Folliculitis                       |                |                 |                |
| subjects affected / exposed        | 1 / 41 (2.44%) | 2 / 33 (6.06%)  | 0 / 12 (0.00%) |
| occurrences (all)                  | 1              | 3               | 0              |
| Pharyngitis                        |                |                 |                |
| subjects affected / exposed        | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                  | 1              | 0               | 0              |
| Pulpitis dental                    |                |                 |                |
| subjects affected / exposed        | 0 / 41 (0.00%) | 0 / 33 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                  | 0              | 0               | 1              |
| Respiratory tract infection        |                |                 |                |
| subjects affected / exposed        | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                  | 1              | 0               | 1              |
| Viral infection                    |                |                 |                |
| subjects affected / exposed        | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                  | 2              | 0               | 0              |
| Tinea manuum                       |                |                 |                |
| subjects affected / exposed        | 0 / 41 (0.00%) | 0 / 33 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                  | 0              | 0               | 1              |
| Tonsillitis                        |                |                 |                |
| subjects affected / exposed        | 2 / 41 (4.88%) | 1 / 33 (3.03%)  | 1 / 12 (8.33%) |
| occurrences (all)                  | 2              | 1               | 1              |
| Vaginal infection                  |                |                 |                |
| subjects affected / exposed        | 1 / 41 (2.44%) | 0 / 33 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                  | 2              | 0               | 1              |
| Respiratory tract infection viral  |                |                 |                |
| subjects affected / exposed        | 0 / 41 (0.00%) | 0 / 33 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                  | 0              | 0               | 1              |
| Metabolism and nutrition disorders |                |                 |                |
| Hypocalcaemia                      |                |                 |                |
| subjects affected / exposed        | 1 / 41 (2.44%) | 4 / 33 (12.12%) | 0 / 12 (0.00%) |
| occurrences (all)                  | 1              | 5               | 0              |

|                                |                |                 |                |
|--------------------------------|----------------|-----------------|----------------|
| Hypernatraemia                 |                |                 |                |
| subjects affected / exposed    | 3 / 41 (7.32%) | 0 / 33 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)              | 3              | 0               | 0              |
| Cerebral salt-wasting syndrome |                |                 |                |
| subjects affected / exposed    | 0 / 41 (0.00%) | 0 / 33 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)              | 0              | 0               | 1              |
| Decreased appetite             |                |                 |                |
| subjects affected / exposed    | 3 / 41 (7.32%) | 8 / 33 (24.24%) | 0 / 12 (0.00%) |
| occurrences (all)              | 3              | 9               | 0              |
| Hypokalaemia                   |                |                 |                |
| subjects affected / exposed    | 1 / 41 (2.44%) | 4 / 33 (12.12%) | 0 / 12 (0.00%) |
| occurrences (all)              | 1              | 9               | 0              |
| Hyperkalaemia                  |                |                 |                |
| subjects affected / exposed    | 2 / 41 (4.88%) | 2 / 33 (6.06%)  | 0 / 12 (0.00%) |
| occurrences (all)              | 2              | 2               | 0              |
| Hyperglycaemia                 |                |                 |                |
| subjects affected / exposed    | 1 / 41 (2.44%) | 3 / 33 (9.09%)  | 0 / 12 (0.00%) |
| occurrences (all)              | 2              | 3               | 0              |
| Hypomagnesaemia                |                |                 |                |
| subjects affected / exposed    | 0 / 41 (0.00%) | 6 / 33 (18.18%) | 0 / 12 (0.00%) |
| occurrences (all)              | 0              | 27              | 0              |
| Hyponatraemia                  |                |                 |                |
| subjects affected / exposed    | 1 / 41 (2.44%) | 2 / 33 (6.06%)  | 0 / 12 (0.00%) |
| occurrences (all)              | 2              | 3               | 0              |
| Hypophosphataemia              |                |                 |                |
| subjects affected / exposed    | 2 / 41 (4.88%) | 3 / 33 (9.09%)  | 1 / 12 (8.33%) |
| occurrences (all)              | 2              | 6               | 3              |
| Obesity                        |                |                 |                |
| subjects affected / exposed    | 0 / 41 (0.00%) | 1 / 33 (3.03%)  | 1 / 12 (8.33%) |
| occurrences (all)              | 0              | 1               | 1              |
| Vitamin D deficiency           |                |                 |                |
| subjects affected / exposed    | 0 / 41 (0.00%) | 0 / 33 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)              | 0              | 0               | 1              |

|                                   |  |  |  |
|-----------------------------------|--|--|--|
| <b>Non-serious adverse events</b> | LGG cohort:<br>dabrafenib +<br>trametinib (On-<br>treatment) |  |  |
|-----------------------------------|--|--|--|

|   |                         |  |  |
|---|-------------------------|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 73 / 73 (100.00%)       |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Skin papilloma<br>subjects affected / exposed<br>occurrences (all) | 10 / 73 (13.70%)<br>18  |  |  |
| Melanocytic naevus<br>subjects affected / exposed<br>occurrences (all)  | 4 / 73 (5.48%)<br>7     |  |  |
| General disorders and administration site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 73 (2.74%)<br>4     |  |  |
| Catheter site pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 73 (0.00%)<br>0     |  |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)  | 4 / 73 (5.48%)<br>4     |  |  |
| Facial pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 73 (1.37%)<br>1     |  |  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)  | 1 / 73 (1.37%)<br>1     |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 25 / 73 (34.25%)<br>38  |  |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)   | 2 / 73 (2.74%)<br>2     |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 51 / 73 (69.86%)<br>239 |  |  |
| Malaise   |                         |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 73 (2.74%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Cyst  |                  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| Gait disturbance                                |                  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Hyperpyrexia                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Non-cardiac chest pain                          |                  |  |  |
| subjects affected / exposed                     | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                               | 6                |  |  |
| Immune system disorders                         |                  |  |  |
| Hypersensitivity                                |                  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Reproductive system and breast disorders        |                  |  |  |
| Pelvic pain                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Nasal congestion                                |                  |  |  |
| subjects affected / exposed                     | 3 / 73 (4.11%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Cough   |                  |  |  |
| subjects affected / exposed                     | 11 / 73 (15.07%) |  |  |
| occurrences (all)                               | 18               |  |  |
| Dysphonia                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Epistaxis                                       |                  |  |  |
| subjects affected / exposed                     | 16 / 73 (21.92%) |  |  |
| occurrences (all)                               | 42               |  |  |
| Oropharyngeal pain                              |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 10 / 73 (13.70%) |  |  |
| occurrences (all)           | 16               |  |  |
| Rhinitis allergic           |                  |  |  |
| subjects affected / exposed | 3 / 73 (4.11%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Rhinorrhoea                 |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Tonsillar hypertrophy       |                  |  |  |
| subjects affected / exposed | 0 / 73 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Dyspnoea                    |                  |  |  |
| subjects affected / exposed | 1 / 73 (1.37%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Snoring                     |                  |  |  |
| subjects affected / exposed | 0 / 73 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Psychiatric disorders       |                  |  |  |
| Anxiety                     |                  |  |  |
| subjects affected / exposed | 1 / 73 (1.37%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Intentional self-injury     |                  |  |  |
| subjects affected / exposed | 0 / 73 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Insomnia                    |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Mental status changes       |                  |  |  |
| subjects affected / exposed | 0 / 73 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Somatic symptom disorder    |                  |  |  |
| subjects affected / exposed | 0 / 73 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Product issues              |                  |  |  |
| Device malfunction          |                  |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed          | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Investigations                       |                  |  |  |
| Aspartate aminotransferase increased |                  |  |  |
| subjects affected / exposed          | 9 / 73 (12.33%)  |  |  |
| occurrences (all)                    | 11               |  |  |
| Blood bicarbonate decreased          |                  |  |  |
| subjects affected / exposed          | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Blood alkaline phosphatase increased |                  |  |  |
| subjects affected / exposed          | 7 / 73 (9.59%)   |  |  |
| occurrences (all)                    | 8                |  |  |
| Alanine aminotransferase increased   |                  |  |  |
| subjects affected / exposed          | 10 / 73 (13.70%) |  |  |
| occurrences (all)                    | 12               |  |  |
| Ejection fraction decreased          |                  |  |  |
| subjects affected / exposed          | 2 / 73 (2.74%)   |  |  |
| occurrences (all)                    | 2                |  |  |
| Lymphocyte count decreased           |                  |  |  |
| subjects affected / exposed          | 5 / 73 (6.85%)   |  |  |
| occurrences (all)                    | 7                |  |  |
| Neutrophil count decreased           |                  |  |  |
| subjects affected / exposed          | 11 / 73 (15.07%) |  |  |
| occurrences (all)                    | 22               |  |  |
| Platelet count decreased             |                  |  |  |
| subjects affected / exposed          | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                    | 6                |  |  |
| SARS-CoV-2 test negative             |                  |  |  |
| subjects affected / exposed          | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                    | 8                |  |  |
| Weight increased                     |                  |  |  |
| subjects affected / exposed          | 12 / 73 (16.44%) |  |  |
| occurrences (all)                    | 13               |  |  |
| Weight decreased                     |                  |  |  |



|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                    | 2 / 73 (2.74%)  |  |  |
| occurrences (all)                              | 3               |  |  |
| White blood cell count decreased               |                 |  |  |
| subjects affected / exposed                    | 9 / 73 (12.33%) |  |  |
| occurrences (all)                              | 17              |  |  |
| Streptococcus test positive                    |                 |  |  |
| subjects affected / exposed                    | 1 / 73 (1.37%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Blood pressure decreased                       |                 |  |  |
| subjects affected / exposed                    | 0 / 73 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| SARS-CoV-2 test positive                       |                 |  |  |
| subjects affected / exposed                    | 6 / 73 (8.22%)  |  |  |
| occurrences (all)                              | 8               |  |  |
| Injury, poisoning and procedural complications |                 |  |  |
| Contusion                                      |                 |  |  |
| subjects affected / exposed                    | 3 / 73 (4.11%)  |  |  |
| occurrences (all)                              | 3               |  |  |
| Procedural pain                                |                 |  |  |
| subjects affected / exposed                    | 2 / 73 (2.74%)  |  |  |
| occurrences (all)                              | 2               |  |  |
| Infusion related reaction                      |                 |  |  |
| subjects affected / exposed                    | 0 / 73 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Head injury                                    |                 |  |  |
| subjects affected / exposed                    | 1 / 73 (1.37%)  |  |  |
| occurrences (all)                              | 1               |  |  |
| Arthropod bite                                 |                 |  |  |
| subjects affected / exposed                    | 2 / 73 (2.74%)  |  |  |
| occurrences (all)                              | 2               |  |  |
| Ligament sprain                                |                 |  |  |
| subjects affected / exposed                    | 0 / 73 (0.00%)  |  |  |
| occurrences (all)                              | 0               |  |  |
| Skin abrasion                                  |                 |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 6 / 73 (8.22%)<br>6    |  |  |
| Tibia fracture<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 73 (0.00%)<br>0    |  |  |
| Cardiac disorders<br>Aortic valve incompetence<br>subjects affected / exposed<br>occurrences (all) | 0 / 73 (0.00%)<br>0    |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)           | 39 / 73 (53.42%)<br>84 |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                      | 8 / 73 (10.96%)<br>11  |  |  |
| Neuralgia<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 73 (0.00%)<br>0    |  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                   | 5 / 73 (6.85%)<br>7    |  |  |
| Peripheral motor neuropathy<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 73 (0.00%)<br>0    |  |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 73 (0.00%)<br>0    |  |  |
| Seizure<br>subjects affected / exposed<br>occurrences (all)  | 4 / 73 (5.48%)<br>4    |  |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 73 (0.00%)<br>0    |  |  |
| Presyncope   |                        |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed          | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Ataxia                               |                  |  |  |
| subjects affected / exposed          | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Blood and lymphatic system disorders |                  |  |  |
| Anaemia                              |                  |  |  |
| subjects affected / exposed          | 14 / 73 (19.18%) |  |  |
| occurrences (all)                    | 21               |  |  |
| Lymphopenia                          |                  |  |  |
| subjects affected / exposed          | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Leukopenia                           |                  |  |  |
| subjects affected / exposed          | 3 / 73 (4.11%)   |  |  |
| occurrences (all)                    | 3                |  |  |
| Neutropenia                          |                  |  |  |
| subjects affected / exposed          | 10 / 73 (13.70%) |  |  |
| occurrences (all)                    | 14               |  |  |
| Thrombocytopenia                     |                  |  |  |
| subjects affected / exposed          | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Iron deficiency anaemia              |                  |  |  |
| subjects affected / exposed          | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Ear and labyrinth disorders          |                  |  |  |
| Vertigo                              |                  |  |  |
| subjects affected / exposed          | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Ear pain                             |                  |  |  |
| subjects affected / exposed          | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Eye disorders                        |                  |  |  |
| Eyelid ptosis                        |                  |  |  |
| subjects affected / exposed          | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Uveitis                              |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 4 / 73 (5.48%)   |  |  |
| occurrences (all)           | 7                |  |  |
| Dry eye                     |                  |  |  |
| subjects affected / exposed | 4 / 73 (5.48%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Eye pain                    |                  |  |  |
| subjects affected / exposed | 3 / 73 (4.11%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Vision blurred              |                  |  |  |
| subjects affected / exposed | 6 / 73 (8.22%)   |  |  |
| occurrences (all)           | 7                |  |  |
| Gastrointestinal disorders  |                  |  |  |
| Abdominal pain              |                  |  |  |
| subjects affected / exposed | 15 / 73 (20.55%) |  |  |
| occurrences (all)           | 27               |  |  |
| Abdominal pain upper        |                  |  |  |
| subjects affected / exposed | 13 / 73 (17.81%) |  |  |
| occurrences (all)           | 18               |  |  |
| Angular cheilitis           |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Aphthous ulcer              |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Dental caries               |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Diarrhoea                   |                  |  |  |
| subjects affected / exposed | 27 / 73 (36.99%) |  |  |
| occurrences (all)           | 43               |  |  |
| Nausea                      |                  |  |  |
| subjects affected / exposed | 21 / 73 (28.77%) |  |  |
| occurrences (all)           | 32               |  |  |
| Constipation                |                  |  |  |
| subjects affected / exposed | 10 / 73 (13.70%) |  |  |
| occurrences (all)           | 21               |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| Vomiting                               |                  |  |  |
| subjects affected / exposed            | 25 / 73 (34.25%) |  |  |
| occurrences (all)                      | 56               |  |  |
| Stomatitis                             |                  |  |  |
| subjects affected / exposed            | 6 / 73 (8.22%)   |  |  |
| occurrences (all)                      | 10               |  |  |
| Dyspepsia                              |                  |  |  |
| subjects affected / exposed            | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                      | 0                |  |  |
| Food poisoning                         |                  |  |  |
| subjects affected / exposed            | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                      | 0                |  |  |
| Toothache                              |                  |  |  |
| subjects affected / exposed            | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                      | 0                |  |  |
| Skin and subcutaneous tissue disorders |                  |  |  |
| Dermatitis acneiform                   |                  |  |  |
| subjects affected / exposed            | 10 / 73 (13.70%) |  |  |
| occurrences (all)                      | 11               |  |  |
| Alopecia                               |                  |  |  |
| subjects affected / exposed            | 2 / 73 (2.74%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Dermatitis                             |                  |  |  |
| subjects affected / exposed            | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                      | 8                |  |  |
| Acne                                   |                  |  |  |
| subjects affected / exposed            | 10 / 73 (13.70%) |  |  |
| occurrences (all)                      | 11               |  |  |
| Dry skin                               |                  |  |  |
| subjects affected / exposed            | 20 / 73 (27.40%) |  |  |
| occurrences (all)                      | 28               |  |  |
| Eczema                                 |                  |  |  |
| subjects affected / exposed            | 13 / 73 (17.81%) |  |  |
| occurrences (all)                      | 14               |  |  |
| Erythema                               |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 12 / 73 (16.44%) |  |  |
| occurrences (all)           | 19               |  |  |
| Keratosis pilaris           |                  |  |  |
| subjects affected / exposed | 1 / 73 (1.37%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Hand dermatitis             |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Ingrowing nail              |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Erythema nodosum            |                  |  |  |
| subjects affected / exposed | 5 / 73 (6.85%)   |  |  |
| occurrences (all)           | 8                |  |  |
| Panniculitis                |                  |  |  |
| subjects affected / exposed | 6 / 73 (8.22%)   |  |  |
| occurrences (all)           | 13               |  |  |
| Papule                      |                  |  |  |
| subjects affected / exposed | 1 / 73 (1.37%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Pruritus                    |                  |  |  |
| subjects affected / exposed | 9 / 73 (12.33%)  |  |  |
| occurrences (all)           | 10               |  |  |
| Urticaria                   |                  |  |  |
| subjects affected / exposed | 6 / 73 (8.22%)   |  |  |
| occurrences (all)           | 9                |  |  |
| Rash maculo-papular         |                  |  |  |
| subjects affected / exposed | 13 / 73 (17.81%) |  |  |
| occurrences (all)           | 16               |  |  |
| Skin hyperpigmentation      |                  |  |  |
| subjects affected / exposed | 1 / 73 (1.37%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Skin striae                 |                  |  |  |
| subjects affected / exposed | 5 / 73 (6.85%)   |  |  |
| occurrences (all)           | 5                |  |  |
| Rash                        |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 14 / 73 (19.18%) |  |  |
| occurrences (all)           | 29               |  |  |
| Dermatitis contact          |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Dyshidrotic eczema          |                  |  |  |
| subjects affected / exposed | 1 / 73 (1.37%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Rash papular                |                  |  |  |
| subjects affected / exposed | 4 / 73 (5.48%)   |  |  |
| occurrences (all)           | 5                |  |  |
| Hyperkeratosis              |                  |  |  |
| subjects affected / exposed | 3 / 73 (4.11%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Rash erythematous           |                  |  |  |
| subjects affected / exposed | 4 / 73 (5.48%)   |  |  |
| occurrences (all)           | 5                |  |  |
| Erythema multiforme         |                  |  |  |
| subjects affected / exposed | 2 / 73 (2.74%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Skin lesion                 |                  |  |  |
| subjects affected / exposed | 4 / 73 (5.48%)   |  |  |
| occurrences (all)           | 11               |  |  |
| Renal and urinary disorders |                  |  |  |
| Haematuria                  |                  |  |  |
| subjects affected / exposed | 3 / 73 (4.11%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Proteinuria                 |                  |  |  |
| subjects affected / exposed | 1 / 73 (1.37%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Endocrine disorders         |                  |  |  |
| Growth hormone deficiency   |                  |  |  |
| subjects affected / exposed | 0 / 73 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Thyroid disorder            |                  |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Arthralgia                                      |                  |  |  |
| subjects affected / exposed                     | 9 / 73 (12.33%)  |  |  |
| occurrences (all)                               | 9                |  |  |
| Back pain                                       |                  |  |  |
| subjects affected / exposed                     | 7 / 73 (9.59%)   |  |  |
| occurrences (all)                               | 11               |  |  |
| Muscular weakness                               |                  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Myalgia   |                  |  |  |
| subjects affected / exposed                     | 7 / 73 (9.59%)   |  |  |
| occurrences (all)                               | 7                |  |  |
| Pain in extremity                               |                  |  |  |
| subjects affected / exposed                     | 13 / 73 (17.81%) |  |  |
| occurrences (all)                               | 21               |  |  |
| Pain in jaw                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Immobilisation syndrome                         |                  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| Infections and infestations                     |                  |  |  |
| Conjunctivitis                                  |                  |  |  |
| subjects affected / exposed                     | 6 / 73 (8.22%)   |  |  |
| occurrences (all)                               | 8                |  |  |
| Gingivitis                                      |                  |  |  |
| subjects affected / exposed                     | 0 / 73 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| Nasopharyngitis                                 |                  |  |  |
| subjects affected / exposed                     | 9 / 73 (12.33%)  |  |  |
| occurrences (all)                               | 18               |  |  |
| COVID-19  |                  |  |  |



|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| subjects affected / exposed       | 26 / 73 (35.62%) |  |  |
| occurrences (all)                 | 29               |  |  |
| Urinary tract infection           |                  |  |  |
| subjects affected / exposed       | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                 | 8                |  |  |
| Upper respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 16 / 73 (21.92%) |  |  |
| occurrences (all)                 | 29               |  |  |
| Rash pustular                     |                  |  |  |
| subjects affected / exposed       | 6 / 73 (8.22%)   |  |  |
| occurrences (all)                 | 8                |  |  |
| Rhinitis                          |                  |  |  |
| subjects affected / exposed       | 7 / 73 (9.59%)   |  |  |
| occurrences (all)                 | 14               |  |  |
| Sinusitis                         |                  |  |  |
| subjects affected / exposed       | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                 | 4                |  |  |
| Paronychia                        |                  |  |  |
| subjects affected / exposed       | 17 / 73 (23.29%) |  |  |
| occurrences (all)                 | 23               |  |  |
| Otitis media                      |                  |  |  |
| subjects affected / exposed       | 2 / 73 (2.74%)   |  |  |
| occurrences (all)                 | 2                |  |  |
| Bronchitis                        |                  |  |  |
| subjects affected / exposed       | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Ear infection                     |                  |  |  |
| subjects affected / exposed       | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                 | 6                |  |  |
| Oral candidiasis                  |                  |  |  |
| subjects affected / exposed       | 1 / 73 (1.37%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Fungal skin infection             |                  |  |  |
| subjects affected / exposed       | 4 / 73 (5.48%)   |  |  |
| occurrences (all)                 | 4                |  |  |
| Gastroenteritis                   |                  |  |  |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| subjects affected / exposed        | 4 / 73 (5.48%) |  |  |
| occurrences (all)                  | 5              |  |  |
| Folliculitis                       |                |  |  |
| subjects affected / exposed        | 3 / 73 (4.11%) |  |  |
| occurrences (all)                  | 4              |  |  |
| Pharyngitis                        |                |  |  |
| subjects affected / exposed        | 6 / 73 (8.22%) |  |  |
| occurrences (all)                  | 8              |  |  |
| Pulpitis dental                    |                |  |  |
| subjects affected / exposed        | 0 / 73 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Respiratory tract infection        |                |  |  |
| subjects affected / exposed        | 1 / 73 (1.37%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Viral infection                    |                |  |  |
| subjects affected / exposed        | 4 / 73 (5.48%) |  |  |
| occurrences (all)                  | 4              |  |  |
| Tinea manuum                       |                |  |  |
| subjects affected / exposed        | 0 / 73 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Tonsillitis                        |                |  |  |
| subjects affected / exposed        | 2 / 73 (2.74%) |  |  |
| occurrences (all)                  | 2              |  |  |
| Vaginal infection                  |                |  |  |
| subjects affected / exposed        | 0 / 73 (0.00%) |  |  |
| occurrences (all)                  | 0              |  |  |
| Respiratory tract infection viral  |                |  |  |
| subjects affected / exposed        | 1 / 73 (1.37%) |  |  |
| occurrences (all)                  | 1              |  |  |
| Metabolism and nutrition disorders |                |  |  |
| Hypocalcaemia                      |                |  |  |
| subjects affected / exposed        | 2 / 73 (2.74%) |  |  |
| occurrences (all)                  | 3              |  |  |
| Hypernatraemia                     |                |  |  |
| subjects affected / exposed        | 3 / 73 (4.11%) |  |  |
| occurrences (all)                  | 4              |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| Cerebral salt-wasting syndrome<br>subjects affected / exposed<br>occurrences (all) | 0 / 73 (0.00%)<br>0 |  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)             | 4 / 73 (5.48%)<br>4 |  |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 73 (4.11%)<br>3 |  |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 73 (2.74%)<br>4 |  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 73 (2.74%)<br>2 |  |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)                | 1 / 73 (1.37%)<br>2 |  |  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 73 (2.74%)<br>3 |  |  |
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 73 (1.37%)<br>2 |  |  |
| Obesity<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 73 (1.37%)<br>1 |  |  |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all)           | 1 / 73 (1.37%)<br>1 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 07 June 2017     | <ul style="list-style-type: none"><li>• Revised the investigational treatment regimen from dabrafenib monotherapy to include trametinib with dabrafenib for children and adolescents with BRAF V600 mutation-positive relapsed or refractory HGG.</li><li>• Guidance provided to the Sponsor by the FDA and CHMP, in addition to updated efficacy data from the ongoing dabrafenib monotherapy study (CDRB436A2102) supported the use of combination treatment in pediatric glioma clinical studies.</li><li>• Safety related changes were also implemented to include:</li><li>• Requirement to obtain informed consent/assent for patients who continued treatment beyond progression per RANO criteria.</li><li>• Added ophthalmic examinations to follow any visual changes in patients receiving trametinib and dabrafenib combination therapy.</li><li>• Updated dose modification guidance for combination treatment.</li><li>• Revised cardiac toxicity monitoring and the conditions for re-starting study treatment per FDA advice.</li><li>• Clarified that skeletal maturation monitoring of wrist or tibia could be assessed by Xray or MRIs.</li><li>• Added the collection of seizure AE on study treatment.</li><li>• Updated the AESIs pertaining to dabrafenib and trametinib.</li></ul>  |
| 23 February 2018 | <ul style="list-style-type: none"><li>• Added a new cohort of BRAF V600 mutant LGG children and adolescent patients whose tumor was unresectable and required systemic treatment. Additionally, the amendment also added a pediatric formulation of dabrafenib as a dispersible tablet.</li><li>• The LGG cohort was added to enroll approximately 102 pediatric patients with BRAF V600 mutant LGG, randomized 2:1 dabrafenib with trametinib vs carboplatin plus vincristine, with overall response rate (PR+CR) as the primary endpoint.</li><li>• In addition, taste questionnaires for trametinib and dabrafenib pediatric formulations were implemented for all patients who received the trametinib oral solution and/or dabrafenib oral suspension. The PROMIS PRO questionnaire was added for the LGG cohort of patients. Sparse PK collection was included for a subset of LGG patients.</li></ul>  |
| 07 August 2018   | <ul style="list-style-type: none"><li>• Changed the age range of patients eligible to enroll in the study from <math>\geq 6</math> to <math>&lt; 18</math> years of age to <math>\geq 12</math> months to <math>&lt; 18</math> years of age. This change was possible as the recommended dose for the combination of dabrafenib with trametinib for patients between 12 months and 6 years of age had been determined.</li><li>• The inclusion and exclusion criteria were updated to clarify the eligible population for the LGG cohort as patients with BRAF V600 mutant LGG, who either have progressive disease following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression. Further, the exclusion criteria specified that LGG patients who had any prior systemic anticancer therapy or antitumor radiotherapy were excluded.</li><li>• The primary endpoint for the HGG cohort was changed from investigator assessment of ORR to central independent review of ORR. This change could lessen the potential for bias that could be introduced due to investigator assessment in a single arm study. Investigator assessment of ORR was therefore added as a secondary endpoint.</li></ul> |

|                  |  |
|------------------|--|
| 11 March 2019    | <ul style="list-style-type: none"> <li>• Added an additional interim analysis of key safety and pharmacokinetics (PK) data of the adolescent patients (ages <math>\geq 12</math> to <math>&lt; 18</math> years) in the HGG cohort to support a health authority request in the first half of 2019 for data in adolescent patients.</li> <li>• In addition, an exclusion criterion was added to exclude patients with history or current evidence of retinal vein occlusion and central serous retinopathy. This exclusion criteria is standard language for all studies with trametinib and was inadvertently omitted from previous versions of CDRB436G2201.</li> <li>• Optional CSF collection was removed. CSF samples were expected to be very limited (1/30 patients provided a sample), hence, the value of the analyses was limited.</li> </ul> |
| 12 December 2019 | <ul style="list-style-type: none"> <li>• Added dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) which had been reported during treatment with dabrafenib in combination with trametinib outside this clinical study. Changed the duration of male and female contraception following the last dose of dabrafenib from 4 weeks to 2 weeks and following the last dose of trametinib from 6 months to 16 weeks.</li> <li>• Further, one of the inclusion criteria was clarified to indicate that local histological diagnosis of HGG was sufficient for study entry and also criteria for patients with Gilbert's syndrome were established.</li> </ul>  |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported