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	v2 (current)
This version publication date	13 March 2024
First version publication date	11 November 2023
Version creation reason	• Correction of full data set Updated to align with CT.gov results disclosure form

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:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	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
Arm title	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 ≥ 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)

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^2 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^2 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)

Arm title	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^2 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^2 as weekly IV infusion over 60 minutes on weeks 1 to 4 of each cycle.

Arm title	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: dabrafenib and trametinib	LGG cohort: carboplatin and vincristine	HGG cohort: dabrafenib and 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: dabrafenib and trametinib	LGG cohort: carboplatin and vincristine	HGG cohort: dabrafenib and 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:	
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)	

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[1]
End point description:	
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. 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: ≥ 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 nonmeasureable 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 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: dabrafenib and trametinib	LGG cohort: carboplatin and 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

Statistical analysis title	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[2]
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[3][4]

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.
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: ≥ 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 nonmeasureable 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

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%)	56.1 (39.7 to 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[5]

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 4weeks; 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 nonmeasureable 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

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: Percentage of participants				
number (confidence interval 95%)				
Up to approx. 3 years	54.8 (42.7 to 66.5)	13.5 (4.5 to 28.8)		
Up to approx. 4.2 years	58.9 (46.8 to 70.3)	18.9 (8.0 to 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[6]

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 4weeks; 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 nonmeasureable 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: dabrafenib and trametinib	LGG cohort: carboplatin and 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[7]

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 4weeks; 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 nonmeasureable 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: dabrafenib and trametinib	LGG cohort: carboplatin and 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[8]

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: 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%)				
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

Statistical analysis title	LGG cohort: PFS analysis
Statistical analysis description:	
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 [9]
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[10]

End point description:

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: 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%)				
Up to approx. 3 years	9999 (-9999 to 9999)	9999 (12.6 to 9999)		
Up to approx 4.2 years	46.0 (38.6 to 9999)	30.8 (7.0 to 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[11]

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 4weeks; 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 nonmeasureable 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: 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%)	11.0 (6.0 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

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[12]

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 4weeks; 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 nonmeasureable 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: 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%)	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 investigator assessment using RANO criteria

End point title	LGG cohort: Clinical Benefit Rate (CBR) by investigator assessment using RANO criteria[13]

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 4weeks; 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 nonmeasureable 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: Partient 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: dabrafenib and trametinib	LGG cohort: carboplatin and 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: 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[14]

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 4weeks; 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 nonmeasureable 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: Partient 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: dabrafenib and trametinib	LGG cohort: carboplatin and 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: Kaplan-Meier Estimates of Overall survival (OS)

End point title	LGG cohort: Kaplan-Meier Estimates of Overall survival (OS)[15]

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[16]

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: dabrafenib and trametinib	LGG cohort: carboplatin and 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 to 100.0)	96.9 (79.8 to 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[17]

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 4weeks; 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 nonmeasureable 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: dabrafenib and 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 73.7)			
Up to approx. 4.8 years	61.0 (44.5 to 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[18]

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 4weeks; 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 nonmeasureable 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

End point values	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[19]

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 4weeks; 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 nonmeasureable 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 Investigatort Assessment using RANO Criteria

End point title	HGG cohort: Kaplan-Meier Estimates of Progression free survival (PFS) as per Investigatort Assessment using RANO Criteria[20]

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:

[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

End point values	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: 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[21]

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 4weeks; 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 nonmeasureable 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

End point values	HGG cohort: dabrafenib and trametinib			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Months				
median (confidence interval 95%)	8.5 (2.0 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[22]

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:

[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

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

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[23]

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 4weeks; 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 nonmeasureable 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: Partient 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

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: 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[24]

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 4weeks; 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 nonmeasureable 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: Partient 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:

[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

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%)	65.9 (49.4 to 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[25]

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 4weeks; 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 nonmeasureable 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:

[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: Months				
median (confidence interval 95%)	3.4 (1.8 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax for trametinib

End point title	Cmax for trametinib[26]

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:

[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

End point values	LGG cohort: dabrafenib and trametinib	HGG cohort: dabrafenib and 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: AUClast for trametinib

End point title	AUClast for trametinib[27]

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:

[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 all arms receiving trametinib

End point values	LGG cohort: dabrafenib and trametinib	HGG cohort: dabrafenib and trametinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	36		
Units: hour (hr) * nanogram (ng)/mililiter (mL)				
geometric mean (geometric coefficient of variation)	328 (± 33.4)	282 (± 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)[28]

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:

[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 the HGG cohort arm

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

Statistical analyses

No statistical analyses for this end point

Secondary: T1/2 for trametinib

End point title	T1/2 for trametinib[29]

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:

[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: dabrafenib and trametinib	HGG cohort: dabrafenib and trametinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	24		
Units: hour				
geometric mean (geometric coefficient of variation)	25.7 (± 37.9)	26.7 (± 62.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau for trametinib

End point title	AUCtau for trametinib[30]

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:

[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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[31]

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:

[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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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: Ctrough for trametinib

End point title	Ctrough for trametinib[32]

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:

[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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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 (± 30.1)	8.73 (± 72.7)		

Statistical analyses

No statistical analyses for this end point

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

End point title	AUClast for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib amd hydroxy-dabrafenib)[33]

End point description:

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:

[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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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 amd hydroxy-dabrafenib)

End point title	Cmax for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib amd hydroxy-dabrafenib)[34]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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 amd hydroxy-dabrafenib)

End point title	AUCtau for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib amd hydroxy-dabrafenib)[35]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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 amd hydroxy-dabrafenib)

End point title	Tmax for dabrafenib and its metabolites (carboxy-dabrafenib, desmethyl-dabrafenib amd hydroxy-dabrafenib)[36]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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 amd hydroxy-dabrafenib)

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

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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)[38]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[39]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[40]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[41]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[42]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[43]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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

No statistical analyses for this end point

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[44]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[45]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[46]

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: dabrafenib and trametinib	HGG cohort: dabrafenib and 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[47]

End point description:

The questionnaire included 7 items measuring the global health of the patient. 4 items used a 5-level Likert scale with 1=poor and 5=excellent; 1 item used a 5-level Likert scale with 1=never and 5=always; and 2 items used a 5-level Likert scale with 1=never and 5=almost always. The total raw global health score, ranging from 7 to 35, was computed by summing item values, with higher scores indicating better overall well-being. Raw scores were then transformed into T-scores, standardized with a mean of 50 and a standard deviation of 10. Higher T-scores reflected better global health status. Participants who discontinued treatment for reasons other than disease progression entered the post-treatment efficacy follow-up phase, where the 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: 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)	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[48]

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. Raw scores were then converted into T-scores, standardized with a mean of 50 and a standard deviation of 10. Higher T-scores indicated more severe pain experiences.
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: 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)	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[49]

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. Raw scores were then converted into T-scores, standardized with a mean of 50 and a standard deviation of 10. Higher T-scores indicated a greater level of reported 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)[50]

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: ≥ 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 nonmeasureable 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: dabrafenib and trametinib	LGG cohort: carboplatin and 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 66.5)	16.2 (6.2 to 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)[51]

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: ≥ 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 nonmeasureable 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

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%)	56.1 (39.7 to 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

End point values	LGG cohort: dabrafenib and trametinib	LGG cohort: carboplatin and vincristine	HGG cohort: dabrafenib and 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 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: 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)

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 crossedover to dabrafenib and trametinib after disease progression (up to 30 days post- crossover treatment)

Serious adverse events	HGG cohort: dabrafenib + trametinib (On-treatment)	LGG cohort: dabrafenib + trametinib (On-treatment)	LGG cohort: carboplatin + vincristine (On-treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 41 (68.29%)	34 / 73 (46.58%)	14 / 33 (42.42%)
number of deaths (all causes)	6	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	12 / 73 (16.44%)	6 / 33 (18.18%)
occurrences causally related to treatment / all	2 / 3	22 / 29	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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 / 73 (0.00%)	0 / 33 (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 / 73 (0.00%)	0 / 33 (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%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Aspiration			

subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Pneumothorax			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Atelectasis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (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
Tonsillar hypertrophy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			

subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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 / 73 (0.00%)	0 / 33 (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 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (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
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Procedural complication			
subjects affected / exposed	0 / 41 (0.00%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Shunt malfunction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tooth avulsion			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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
Fracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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
Road traffic accident			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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
Altered state of consciousness			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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
Cerebral ventricle dilatation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrospinal fluid circulation disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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

Dizziness			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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 / 73 (0.00%)	0 / 33 (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%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	3 / 41 (7.32%)	1 / 73 (1.37%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 4	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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 / 73 (0.00%)	0 / 33 (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%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (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
Partial seizures			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 41 (4.88%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	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 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (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
Syncope			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
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%)	1 / 73 (1.37%)	0 / 33 (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
Papilloedema			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 41 (2.44%)	3 / 73 (4.11%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Pancreatitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rash			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (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
Nephrolithiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Encephalomyelitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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 / 73 (1.37%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (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
Toxic shock syndrome			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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 abscess			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	3 / 73 (4.11%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 41 (0.00%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral myositis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Haematological infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (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 / 73 (0.00%)	0 / 33 (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
Pneumonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (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
Hypernatraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LGG cohort: carboplatin+ vincristine (Crossover On-treatment)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)		
number of deaths (all causes)	1		

number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	0 / 12 (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 / 12 (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	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atelectasis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillar hypertrophy				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Agitation				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anxiety				

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	0 / 12 (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 / 12 (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 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oxygen saturation decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural complication			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Shunt malfunction				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth avulsion				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	0 / 12 (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 / 12 (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 / 12 (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 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral ventricle dilatation				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrospinal fluid circulation disorder				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Depressed level of consciousness				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial paralysis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine with aura				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic cerebral infarction				

subjects affected / exposed	0 / 12 (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 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paresis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	0 / 12 (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 / 12 (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 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				

subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Central nervous system lesion				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Optic perineuritis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 12 (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 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 12 (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	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Papilloedema				
subjects affected / exposed	0 / 12 (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 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 12 (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 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 12 (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	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	0 / 12 (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	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalomyelitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain abscess				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic shock syndrome				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	0 / 12 (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	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral myositis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematological infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vulvitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypernatraemia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	HGG cohort: dabrafenib + trametinib (On-treatment)	LGG cohort: dabrafenib + trametinib (On-treatment)	LGG cohort: carboplatin + vincristine (On-treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	73 / 73 (100.00%)	33 / 33 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	4 / 41 (9.76%)	10 / 73 (13.70%)	0 / 33 (0.00%)
occurrences (all)	6	18	0
Melanocytic naevus			
subjects affected / exposed	2 / 41 (4.88%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	3	7	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 73 (2.74%)	3 / 33 (9.09%)
occurrences (all)	3	4	5
Catheter site pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	3
Chills			
subjects affected / exposed	1 / 41 (2.44%)	4 / 73 (5.48%)	1 / 33 (3.03%)
occurrences (all)	2	4	1
Facial pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	3 / 33 (9.09%)
occurrences (all)	0	1	5
Influenza like illness			
subjects affected / exposed	1 / 41 (2.44%)	1 / 73 (1.37%)	2 / 33 (6.06%)
occurrences (all)	1	1	2
Fatigue			
subjects affected / exposed	6 / 41 (14.63%)	25 / 73 (34.25%)	10 / 33 (30.30%)
occurrences (all)	7	38	16
Oedema peripheral			
subjects affected / exposed	4 / 41 (9.76%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	7	2	0

Pyrexia			
subjects affected / exposed	20 / 41 (48.78%)	51 / 73 (69.86%)	2 / 33 (6.06%)
occurrences (all)	81	239	4
Malaise			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	1	3	0
Cyst			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Hyperpyrexia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 41 (4.88%)	4 / 73 (5.48%)	2 / 33 (6.06%)
occurrences (all)	3	6	3
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 41 (2.44%)	1 / 73 (1.37%)	6 / 33 (18.18%)
occurrences (all)	1	1	8
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	4 / 41 (9.76%)	3 / 73 (4.11%)	2 / 33 (6.06%)
occurrences (all)	4	4	3
Cough			
subjects affected / exposed	7 / 41 (17.07%)	11 / 73 (15.07%)	4 / 33 (12.12%)
occurrences (all)	9	18	7
Dysphonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	2 / 33 (6.06%)
occurrences (all)	0	1	2

Epistaxis			
subjects affected / exposed	6 / 41 (14.63%)	16 / 73 (21.92%)	1 / 33 (3.03%)
occurrences (all)	7	42	2
Oropharyngeal pain			
subjects affected / exposed	6 / 41 (14.63%)	10 / 73 (13.70%)	7 / 33 (21.21%)
occurrences (all)	6	16	8
Rhinitis allergic			
subjects affected / exposed	0 / 41 (0.00%)	3 / 73 (4.11%)	2 / 33 (6.06%)
occurrences (all)	0	4	2
Rhinorrhoea			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	4 / 33 (12.12%)
occurrences (all)	1	2	4
Tonsillar hypertrophy			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	2 / 41 (4.88%)	1 / 73 (1.37%)	2 / 33 (6.06%)
occurrences (all)	3	1	2
Snoring			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 41 (4.88%)	1 / 73 (1.37%)	5 / 33 (15.15%)
occurrences (all)	2	1	6
Intentional self-injury			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	3 / 41 (7.32%)	2 / 73 (2.74%)	1 / 33 (3.03%)
occurrences (all)	4	4	1
Mental status changes			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Somatic symptom disorder			

subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Product issues			
Device malfunction			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 41 (7.32%)	9 / 73 (12.33%)	5 / 33 (15.15%)
occurrences (all)	3	11	15
Blood bicarbonate decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	3 / 33 (9.09%)
occurrences (all)	0	0	9
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 41 (7.32%)	7 / 73 (9.59%)	1 / 33 (3.03%)
occurrences (all)	4	8	1
Alanine aminotransferase increased			
subjects affected / exposed	4 / 41 (9.76%)	10 / 73 (13.70%)	9 / 33 (27.27%)
occurrences (all)	5	12	18
Ejection fraction decreased			
subjects affected / exposed	4 / 41 (9.76%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	4	2	0
Lymphocyte count decreased			
subjects affected / exposed	3 / 41 (7.32%)	5 / 73 (6.85%)	5 / 33 (15.15%)
occurrences (all)	4	7	16
Neutrophil count decreased			
subjects affected / exposed	2 / 41 (4.88%)	11 / 73 (15.07%)	16 / 33 (48.48%)
occurrences (all)	13	22	43
Platelet count decreased			
subjects affected / exposed	1 / 41 (2.44%)	4 / 73 (5.48%)	10 / 33 (30.30%)
occurrences (all)	1	6	29
SARS-CoV-2 test negative			
subjects affected / exposed	2 / 41 (4.88%)	4 / 73 (5.48%)	1 / 33 (3.03%)
occurrences (all)	2	8	1
Weight increased			

subjects affected / exposed	6 / 41 (14.63%)	12 / 73 (16.44%)	0 / 33 (0.00%)
occurrences (all)	6	13	0
Weight decreased			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	4 / 33 (12.12%)
occurrences (all)	1	3	4
White blood cell count decreased			
subjects affected / exposed	5 / 41 (12.20%)	9 / 73 (12.33%)	12 / 33 (36.36%)
occurrences (all)	8	17	43
Streptococcus test positive			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Blood pressure decreased			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 41 (0.00%)	6 / 73 (8.22%)	1 / 33 (3.03%)
occurrences (all)	0	8	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 41 (4.88%)	3 / 73 (4.11%)	3 / 33 (9.09%)
occurrences (all)	3	3	3
Procedural pain			
subjects affected / exposed	0 / 41 (0.00%)	2 / 73 (2.74%)	2 / 33 (6.06%)
occurrences (all)	0	2	2
Infusion related reaction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	5 / 33 (15.15%)
occurrences (all)	0	0	8
Head injury			
subjects affected / exposed	3 / 41 (7.32%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	3	1	0
Arthropod bite			
subjects affected / exposed	3 / 41 (7.32%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	5	2	0
Ligament sprain			

subjects affected / exposed	2 / 41 (4.88%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Skin abrasion			
subjects affected / exposed	0 / 41 (0.00%)	6 / 73 (8.22%)	1 / 33 (3.03%)
occurrences (all)	0	6	1
Tibia fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 41 (41.46%)	39 / 73 (53.42%)	8 / 33 (24.24%)
occurrences (all)	62	84	14
Dizziness			
subjects affected / exposed	4 / 41 (9.76%)	8 / 73 (10.96%)	0 / 33 (0.00%)
occurrences (all)	4	11	0
Neuralgia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	3 / 33 (9.09%)
occurrences (all)	0	0	3
Paraesthesia			
subjects affected / exposed	3 / 41 (7.32%)	5 / 73 (6.85%)	3 / 33 (9.09%)
occurrences (all)	3	7	3
Peripheral motor neuropathy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	5 / 33 (15.15%)
occurrences (all)	0	0	5
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	5 / 33 (15.15%)
occurrences (all)	0	0	5
Seizure			
subjects affected / exposed	5 / 41 (12.20%)	4 / 73 (5.48%)	2 / 33 (6.06%)
occurrences (all)	11	4	12
Neuropathy peripheral			

subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Presyncope			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Ataxia			
subjects affected / exposed	3 / 41 (7.32%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	3	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 41 (9.76%)	14 / 73 (19.18%)	20 / 33 (60.61%)
occurrences (all)	6	21	56
Lymphopenia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	3	0	0
Leukopenia			
subjects affected / exposed	3 / 41 (7.32%)	3 / 73 (4.11%)	2 / 33 (6.06%)
occurrences (all)	4	3	8
Neutropenia			
subjects affected / exposed	7 / 41 (17.07%)	10 / 73 (13.70%)	10 / 33 (30.30%)
occurrences (all)	8	14	29
Thrombocytopenia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 73 (1.37%)	5 / 33 (15.15%)
occurrences (all)	1	1	17
Iron deficiency anaemia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 41 (2.44%)	4 / 73 (5.48%)	2 / 33 (6.06%)
occurrences (all)	1	4	2
Ear pain			
subjects affected / exposed	1 / 41 (2.44%)	4 / 73 (5.48%)	1 / 33 (3.03%)
occurrences (all)	1	4	1
Eye disorders			

Eyelid ptosis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Uveitis			
subjects affected / exposed	1 / 41 (2.44%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	1	7	0
Dry eye			
subjects affected / exposed	2 / 41 (4.88%)	4 / 73 (5.48%)	1 / 33 (3.03%)
occurrences (all)	4	4	1
Eye pain			
subjects affected / exposed	1 / 41 (2.44%)	3 / 73 (4.11%)	0 / 33 (0.00%)
occurrences (all)	1	3	0
Vision blurred			
subjects affected / exposed	1 / 41 (2.44%)	6 / 73 (8.22%)	1 / 33 (3.03%)
occurrences (all)	1	7	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 41 (12.20%)	15 / 73 (20.55%)	7 / 33 (21.21%)
occurrences (all)	10	27	13
Abdominal pain upper			
subjects affected / exposed	2 / 41 (4.88%)	13 / 73 (17.81%)	2 / 33 (6.06%)
occurrences (all)	2	18	3
Angular cheilitis			
subjects affected / exposed	3 / 41 (7.32%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	4	2	0
Aphthous ulcer			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Dental caries			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	10 / 41 (24.39%)	27 / 73 (36.99%)	6 / 33 (18.18%)
occurrences (all)	12	43	7
Nausea			

subjects affected / exposed	11 / 41 (26.83%)	21 / 73 (28.77%)	17 / 33 (51.52%)
occurrences (all)	17	32	33
Constipation			
subjects affected / exposed	6 / 41 (14.63%)	10 / 73 (13.70%)	12 / 33 (36.36%)
occurrences (all)	9	21	14
Vomiting			
subjects affected / exposed	12 / 41 (29.27%)	25 / 73 (34.25%)	17 / 33 (51.52%)
occurrences (all)	23	56	61
Stomatitis			
subjects affected / exposed	3 / 41 (7.32%)	6 / 73 (8.22%)	5 / 33 (15.15%)
occurrences (all)	3	10	7
Dyspepsia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Food poisoning			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	2 / 41 (4.88%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	4 / 41 (9.76%)	10 / 73 (13.70%)	0 / 33 (0.00%)
occurrences (all)	5	11	0
Alopecia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	9 / 33 (27.27%)
occurrences (all)	1	2	9
Dermatitis			
subjects affected / exposed	3 / 41 (7.32%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	3	8	0
Acne			
subjects affected / exposed	6 / 41 (14.63%)	10 / 73 (13.70%)	0 / 33 (0.00%)
occurrences (all)	9	11	0
Dry skin			
subjects affected / exposed	14 / 41 (34.15%)	20 / 73 (27.40%)	1 / 33 (3.03%)
occurrences (all)	17	28	1

Eczema			
subjects affected / exposed	5 / 41 (12.20%)	13 / 73 (17.81%)	0 / 33 (0.00%)
occurrences (all)	9	14	0
Erythema			
subjects affected / exposed	5 / 41 (12.20%)	12 / 73 (16.44%)	0 / 33 (0.00%)
occurrences (all)	6	19	0
Keratosis pilaris			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Hand dermatitis			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Ingrowing nail			
subjects affected / exposed	3 / 41 (7.32%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	3	2	0
Erythema nodosum			
subjects affected / exposed	3 / 41 (7.32%)	5 / 73 (6.85%)	0 / 33 (0.00%)
occurrences (all)	9	8	0
Panniculitis			
subjects affected / exposed	0 / 41 (0.00%)	6 / 73 (8.22%)	0 / 33 (0.00%)
occurrences (all)	0	13	0
Papule			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	4 / 41 (9.76%)	9 / 73 (12.33%)	2 / 33 (6.06%)
occurrences (all)	5	10	2
Urticaria			
subjects affected / exposed	5 / 41 (12.20%)	6 / 73 (8.22%)	2 / 33 (6.06%)
occurrences (all)	5	9	2
Rash maculo-papular			
subjects affected / exposed	6 / 41 (14.63%)	13 / 73 (17.81%)	0 / 33 (0.00%)
occurrences (all)	11	16	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0

Skin striae			
subjects affected / exposed	1 / 41 (2.44%)	5 / 73 (6.85%)	0 / 33 (0.00%)
occurrences (all)	1	5	0
Rash			
subjects affected / exposed	9 / 41 (21.95%)	14 / 73 (19.18%)	3 / 33 (9.09%)
occurrences (all)	21	29	4
Dermatitis contact			
subjects affected / exposed	3 / 41 (7.32%)	2 / 73 (2.74%)	0 / 33 (0.00%)
occurrences (all)	3	2	0
Dyshidrotic eczema			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	0 / 41 (0.00%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	0	5	0
Hyperkeratosis			
subjects affected / exposed	0 / 41 (0.00%)	3 / 73 (4.11%)	1 / 33 (3.03%)
occurrences (all)	0	4	1
Rash erythematous			
subjects affected / exposed	2 / 41 (4.88%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	2	5	0
Erythema multiforme			
subjects affected / exposed	2 / 41 (4.88%)	2 / 73 (2.74%)	2 / 33 (6.06%)
occurrences (all)	2	2	2
Skin lesion			
subjects affected / exposed	2 / 41 (4.88%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	5	11	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 41 (7.32%)	3 / 73 (4.11%)	2 / 33 (6.06%)
occurrences (all)	3	3	5
Proteinuria			
subjects affected / exposed	1 / 41 (2.44%)	1 / 73 (1.37%)	2 / 33 (6.06%)
occurrences (all)	4	1	2
Endocrine disorders			

Growth hormone deficiency			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Thyroid disorder			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 41 (7.32%)	9 / 73 (12.33%)	1 / 33 (3.03%)
occurrences (all)	3	9	1
Back pain			
subjects affected / exposed	3 / 41 (7.32%)	7 / 73 (9.59%)	4 / 33 (12.12%)
occurrences (all)	5	11	4
Muscular weakness			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	2 / 33 (6.06%)
occurrences (all)	0	1	3
Myalgia			
subjects affected / exposed	3 / 41 (7.32%)	7 / 73 (9.59%)	3 / 33 (9.09%)
occurrences (all)	5	7	4
Pain in extremity			
subjects affected / exposed	4 / 41 (9.76%)	13 / 73 (17.81%)	4 / 33 (12.12%)
occurrences (all)	4	21	4
Pain in jaw			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	6 / 33 (18.18%)
occurrences (all)	0	1	8
Immobilisation syndrome			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	4 / 41 (9.76%)	6 / 73 (8.22%)	2 / 33 (6.06%)
occurrences (all)	4	8	2
Gingivitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			

subjects affected / exposed	2 / 41 (4.88%)	9 / 73 (12.33%)	2 / 33 (6.06%)
occurrences (all)	2	18	2
COVID-19			
subjects affected / exposed	6 / 41 (14.63%)	26 / 73 (35.62%)	0 / 33 (0.00%)
occurrences (all)	7	29	0
Urinary tract infection			
subjects affected / exposed	3 / 41 (7.32%)	4 / 73 (5.48%)	2 / 33 (6.06%)
occurrences (all)	4	8	2
Upper respiratory tract infection			
subjects affected / exposed	10 / 41 (24.39%)	16 / 73 (21.92%)	1 / 33 (3.03%)
occurrences (all)	13	29	2
Rash pustular			
subjects affected / exposed	1 / 41 (2.44%)	6 / 73 (8.22%)	0 / 33 (0.00%)
occurrences (all)	1	8	0
Rhinitis			
subjects affected / exposed	4 / 41 (9.76%)	7 / 73 (9.59%)	4 / 33 (12.12%)
occurrences (all)	5	14	4
Sinusitis			
subjects affected / exposed	2 / 41 (4.88%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	2	4	0
Paronychia			
subjects affected / exposed	3 / 41 (7.32%)	17 / 73 (23.29%)	0 / 33 (0.00%)
occurrences (all)	3	23	0
Otitis media			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	2 / 33 (6.06%)
occurrences (all)	1	2	2
Bronchitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 41 (0.00%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	0	6	0
Oral candidiasis			
subjects affected / exposed	1 / 41 (2.44%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Fungal skin infection			

subjects affected / exposed	0 / 41 (0.00%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	0	4	0
Gastroenteritis			
subjects affected / exposed	2 / 41 (4.88%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	2	5	0
Folliculitis			
subjects affected / exposed	1 / 41 (2.44%)	3 / 73 (4.11%)	2 / 33 (6.06%)
occurrences (all)	1	4	3
Pharyngitis			
subjects affected / exposed	1 / 41 (2.44%)	6 / 73 (8.22%)	0 / 33 (0.00%)
occurrences (all)	1	8	0
Pulpitis dental			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Viral infection			
subjects affected / exposed	1 / 41 (2.44%)	4 / 73 (5.48%)	0 / 33 (0.00%)
occurrences (all)	2	4	0
Tinea manuum			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	2 / 41 (4.88%)	2 / 73 (2.74%)	1 / 33 (3.03%)
occurrences (all)	2	2	1
Vaginal infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	4 / 33 (12.12%)
occurrences (all)	1	3	5

Hypernatraemia			
subjects affected / exposed	3 / 41 (7.32%)	3 / 73 (4.11%)	0 / 33 (0.00%)
occurrences (all)	3	4	0
Cerebral salt-wasting syndrome			
subjects affected / exposed	0 / 41 (0.00%)	0 / 73 (0.00%)	0 / 33 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	3 / 41 (7.32%)	4 / 73 (5.48%)	8 / 33 (24.24%)
occurrences (all)	3	4	9
Hypokalaemia			
subjects affected / exposed	1 / 41 (2.44%)	3 / 73 (4.11%)	4 / 33 (12.12%)
occurrences (all)	1	3	9
Hyperkalaemia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 73 (2.74%)	2 / 33 (6.06%)
occurrences (all)	2	4	2
Hyperglycaemia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	3 / 33 (9.09%)
occurrences (all)	2	2	3
Hypomagnesaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	6 / 33 (18.18%)
occurrences (all)	0	2	27
Hyponatraemia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 73 (2.74%)	2 / 33 (6.06%)
occurrences (all)	2	3	3
Hypophosphataemia			
subjects affected / exposed	2 / 41 (4.88%)	1 / 73 (1.37%)	3 / 33 (9.09%)
occurrences (all)	2	2	6
Obesity			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	1 / 33 (3.03%)
occurrences (all)	0	1	1
Vitamin D deficiency			
subjects affected / exposed	0 / 41 (0.00%)	1 / 73 (1.37%)	0 / 33 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	LGG cohort: carboplatin+ vincristine (Crossover On-		

	treatment)		
Total subjects affected by non-serious adverse events subjects affected / exposed	11 / 12 (91.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Melanocytic naevus			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Catheter site pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Facial pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	50		
Malaise			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cyst			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hyperpyrexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	6		
Dysphonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Oropharyngeal pain			

subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	5		
Rhinitis allergic			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Snoring			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Intentional self-injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Mental status changes			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Somatic symptom disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Product issues			
Device malfunction			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Blood bicarbonate decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Ejection fraction decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
SARS-CoV-2 test negative			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Weight increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Weight decreased			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Streptococcus test positive			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood pressure decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infusion related reaction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Head injury			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin abrasion			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Tibia fracture			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			
Aortic valve incompetence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	10		
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Seizure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Presyncope			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Ataxia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Lymphopenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Iron deficiency anaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ear pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Uveitis			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Angular cheilitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Aphthous ulcer			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Vomiting				
subjects affected / exposed	6 / 12 (50.00%)			
occurrences (all)	10			
Stomatitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Food poisoning				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Toothache				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Skin and subcutaneous tissue disorders				
Dermatitis acneiform				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Alopecia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Dermatitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Acne				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Eczema				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Erythema				

subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Keratosis pilaris				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Hand dermatitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Ingrowing nail				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Erythema nodosum				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Panniculitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Papule				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Pruritus				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Urticaria				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Rash maculo-papular				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Skin hyperpigmentation				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Skin striae				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Rash				

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Dyshidrotic eczema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash papular			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperkeratosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Erythema multiforme			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin lesion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Proteinuria			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Growth hormone deficiency			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Thyroid disorder			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Pain in jaw			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Immobilisation syndrome			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gingivitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
COVID-19			

subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	4			
Urinary tract infection				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Upper respiratory tract infection				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Rash pustular				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	3			
Sinusitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Otitis media				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Bronchitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Ear infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Oral candidiasis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Fungal skin infection				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Gastroenteritis				

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pulpitis dental			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tinea manuum			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vaginal infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypernatraemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		

Cerebral salt-wasting syndrome			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Obesity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2017	• 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. • 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. • Safety related changes were also implemented to include: • Requirement to obtain informed consent/assent for patients who continued treatment beyond progression per RANO criteria. • Added ophthalmic examinations to follow any visual changes in patients receiving trametinib and dabrafenib combination therapy. • Updated dose modification guidance for combination treatment. • Revised cardiac toxicity monitoring and the conditions for re-starting study treatment per FDA advice. • Clarified that skeletal maturation monitoring of wrist or tibia could be assessed by Xray or MRIs. • Added the collection of seizure AE on study treatment. • Updated the AESIs pertaining to dabrafenib and trametinib.
23 February 2018	• 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. • 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. • 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.
07 August 2018	• Changed the age range of patients eligible to enroll in the study from ≥ 6 to < 18 years of age to ≥ 12 months to < 18 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. • 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. • 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.

11 March 2019	• Added an additional interim analysis of key safety and pharmacokinetics (PK) data of the adolescent patients (ages ≥ 12 to < 18 years) in the HGG cohort to support a health authority request in the first half of 2019 for data in adolescent patients. • 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. • 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.
12 December 2019	• 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. • 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported