NOVARTIS

Clinical Development

DRB436/Dabrafenib, TMT212/Trametinib

CDRB436G2201 / NCT02684058

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)

Statistical Analysis Plan (SAP) for HGG cohort

Final CSR

Author:	Trial Statistician
Document type:	SAP Documentation
Document status:	Final
Release date:	17-May-2023
Number of pages:	56

Document History – Changes compared to previous final version of SAP

Version	Date	Changes
Final 1.0	17-May-2023	

Table of contents

List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
BID	*bis in diem*/twice a day
BOR	Best Overall response
CBR	Clinical Benefit Rate
CI	Confidence Interval
CR	Complete Response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
DAR	Dose Administration Record
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
eCRS	Electronic Case Retrieval Strategy
ECHO	Echocardiogram
EoT	End of Treatment
FAS	Full Analysis Set
HGG	High Grade Glioma
LGG	Low Grade Glioma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NMQ	Novartis MedDRA Query
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
QT	Q to T interval (ECG)
QTcF	QT interval corrected using Fridericia method
RANO	Response Assessment in Neuro-Oncology
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDS	Standard Deviation Score
SOC	System Organ Class
SMQ	Standardized MedDRA Query

TBIL	Total bilirubin
TTR	Time To Response
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cells
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the High Grade Glioma (HGG) cohort of the final clinical study report (CSR) of study CDRB436G2201, a multi-center, global, single-arm, open-label, Phase II study conducted in children and adolescent patients with BRAF V600 mutation positive, (a) Low Grade Glioma (LGG), or (b) refractory or relapsed HGG after having received at least one previous standard therapy. This SAP will be used for the final analysis for the HGG cohort. All planned analyses for the LGG cohort are described in a separate SAP.

The content of this SAP is based on protocol CDRB436G2201 amendment version 05. All decisions regarding the final analysis, as defined in this SAP, have been made prior to the final database lock.

1.1 Study design

This study combines two pediatric glioma cohorts (HGG and LGG) into a single multi-center, open-label, phase II study.

The HGG cohort is a multi-center, single-arm, open-label, Phase II study conducted in children and adolescent patients with BRAF mutation positive, refractory or relapsed HGG tumors after having received at least one previous standard therapy. BRAF V600 mutation-positive tumor was assessed locally, or at a Novartis designated central reference laboratory if local BRAF V600 testing was unavailable. Approximately 40 patients will be enrolled to receive dabrafenib and trametinib.

The primary objective is to evaluate the antitumor activity of dabrafenib in combination with trametinib, as measured by the overall response rate (ORR) to study treatment by independent central review assessment using response assessment in neuro-oncology (RANO) criteria in the Full Analysis Set (FAS) population. ORR as assessed through investigator review, duration of response (DOR), time to response (TTR), progression-free survival (PFS), clinical benefit rate (CBR) assessed by investigator and independent central review, overall survival (OS), palatability, pharmacokinetics (PK), and the safety and tolerability profile of dabrafenib and trametinib are secondary endpoints.

Patients may continue to receive the assigned study treatment until disease progression by RANO criteria or loss of clinical benefit as determined by the investigator, unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, or study is terminated by the sponsor.

Patients who have disease progression by RANO criteria may continue study treatment if the investigator determines that patient has clear evidence of clinical benefit from study treatment, continuing study treatment may be in the best interest for the patient, and the patient/legal guardian is willing to continue on study treatment and sign the informed consent for treatment beyond progression. The decision to continue study treatment after progressive disease (PD) must be documented in the patient records and electronic case report forms (eCRF) after every tumor evaluation. In this case, the patient will continue assessments as defined in the study

[Protocol Section 7]. An end of treatment visit will be performed when patients permanently discontinue study treatment.

Patients who discontinue the study treatment without disease progression by RANO criteria will continue tumor assessments as outlined in the study protocol section 7 until documented centrally confirmed disease progression by RANO criteria or death irrespective of start of new anti-neoplastic therapy.

Patients who discontinue study treatment and efficacy follow-up will enter a follow-up period during which survival will be collected every 3 months. During the survival follow-up, subsequent anti-neoplastic therapies initiated after study treatment discontinuation will be collected.

The final analysis will be performed when all patients in both cohorts have been followed for survival for at least 2 years from last patient first study treatment, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

1.2 Study objectives and endpoints

A list of all study objectives and endpoints is given below. For the final CSR, not all study objectives will be reported, as they have already been analyzed in the primary analysis. This is documented in the corresponding SAP section for each objective.

Objective	Endpoint
Primary	
To evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria.	ORR, proportion of patients with a best overall confirmed Complete Response (CR) or Partial Response (PR) by independent review assessment per Response Assessment in Neuro-Oncology (RANO) criteria.
Secondary	
a) Evaluate ORR by investigator assessment b) Evaluate duration of response (DOR) by investigator and central independent review c) Evaluate progression free survival (PFS) by investigator and central independent review d) Evaluate time to response (TTR) by investigator and central independent review e) Evaluate clinical benefit rate (CBR) by investigator and central independent review f) Evaluate overall survival (OS) g) Evaluate the safety and tolerability profile of dabrafenib in combination with trametinib in children and adolescents h) Evaluate the palatability of dabrafenib oral suspension and trametinib oral solution i) Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population	1. ORR by investigator assessment per RANO criteria 2. DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria. 3. PFS, defined as time from first dose of study treatment to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria

Objective	Endpoint
	4. TTR, calculated as the time from the start date of study treatment to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria 5. CBR is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of at least 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria. 6. OS, defined as the time from first dose of study treatment to death due to any cause 7. Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO 8. Palatability questionnaire data 9. Plasma concentration-time profiles of dabrafenib, its metabolites and trametinib and PK parameters
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

A unique cut-off date will be determined for the final analysis, corresponding to the last patient last visit date on the study. The analysis cut-off date will be established at the end of the study when all patients in both cohorts have been followed-up for survival for at least 2 years from last patient first treatment, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event [AE]) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations. Note that for the final analysis, the cut-off date will be defined such that no data are collected beyond the cut-off date, i.e. all collected data will be included in the analysis.

All events with start date before or on the cut-off date and not having a documented end date will be reported as 'ongoing'. This approach applies, in particular, to AE and concomitant medication records.

General analysis conventions

Pooling of centers: unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by frequency counts and percentages; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

Study treatment will refer to dabrafenib and trametinib combination. ***Study drug*** will refer to each component of study treatment.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered as per the Dosage Administration

eCRF. (Example: if first dose of dabrafenib is administered on 05-Jan-2015, and first dose of trametinib is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015). For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered as per Dose Administration Record (DAR) eCRF (Example: if the last dabrafenib dose is administered on 15-Apr-2014, and the last dose of trametinib is administered on 17-Apr-2014, then the date of last administration of study treatment is on 17-Apr-2014).

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, PK, performance status etc.) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as the baseline assessment. In the rare case that time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline. If there is more than one record on the same day of screening the highest value would be considered as baseline. For laboratory data, if there is more than one record on the same day of screening, then records from central laboratory should take precedence over local laboratory records.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For safety reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Notes: if data on clock time is available in the clinical database (e.g. for time of blood/urine sample taken, electrocardiogram (ECG) performed, etc. and first study treatment administration), a more precise distinction between pre-treatment and on-treatment periods is encouraged to be used. If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize Karnofsky/Lansky performance status, physical exam, vital signs, ECG, and laboratory data collected over time (including unscheduled visits), the assessments will be time slotted. Time windows will be defined for descriptive summary by visit. The following general rule will be applied in creating the assessment windows: if more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If two or more assessments within a time window are equidistant from the target date or on the same date, then the maximum will be used. For growth and ECG analysis, if two assessments within a time window are equidistant from the target date or on the same date then the mean will be used. For laboratory data, if two assessments within a time window are equidistant from the target date or on the same date, then records from central laboratory should take precedence over local laboratory records. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for Karnofsky/Lansky performance status/Urinalysis

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1[a]	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57

Time Window	Planned Visit Timing	Time Window Definition
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7 .
End of treatment (EoT)		
EoT	Within 30 days after last dose	Earliest data available on or after EoT date up to and including 30 days after EoT
Post treatment[b]		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14
[a]Study Day 1 = start date of study treatment [b]Post treatment study day 1=end of treatment date + 1 day		

Table 2-2 Time windows for physical exam/vital signs/hematology/chemistry

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1[a]	≤ Study Day 1
Week 2 Day 1	Study Day 8	Study Days 6 – 10
Week 3 Day 1	Study Day 15	Study Days 13 – 17
Week 4 Day 1	Study Day 22	Study Days 20 – 24
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7
End of treatment (EoT)		
EoT	Within 30 days after last dose	Earliest data available on or

Time Window	Planned Visit Timing	Time Window Definition
		after EoT date up to and including 30 days after EoT
Post treatment[b]		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7 30	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14

[a]Study Day 1 = start date of study treatment
[b]Post treatment study day 1=end of treatment date + 1 day

Table 2-3 Time windows for ECG/Visual Acuity

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1[a]	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 16 Day 1	Study Day 106	Study Days 99 – 113
Week 32 Day 1	Study Day 218	Study Days 211 – 225
Week 48 Day 1	Study Day 330	Study Days 323 – 337
Week 72 Day 1	Study Day 498	Study Days 491 – 505
Every 16 weeks thereafter		
Week y=16+16*k (with k = 1, 2, …)	Study Day (16+16*k-1)*7+1	Study Day (16+16*k-1)*7+1-7 to (16+16*k-1)*7+1+7
End of treatment (EoT)		
EoT	Within 30 days after last dose	Earliest data available on or after EoT date up to and including 30 days after EoT

[a]Study Day 1 = start date of study treatment

For all analyses regarding abnormal assessments or analyses based on worst or best post-baseline value (laboratory, ECGs, vital signs, Karnofsky/Lansky performance status, echocardiogram (ECHO), ophthalmologic exam, dermatologic exam, etc.), all post-baseline values will be included (scheduled, unscheduled, repeat).

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the sources specified in Table 2-4.

Table 2-4 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RANO) assessment date	Evaluation is marked as 'done'.
Laboratory dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will NOT be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a DAR) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF. If the day is missing from the date of last contact, it will be imputed to the 15th day of the month and year of last contact only if derived from the survival page.

The last contact date will be used for censoring of patients in the analysis of OS.

2.2 Analysis sets

Full Analysis Set

The **Full Analysis Set** (FAS) comprises all patients to whom study treatment has been assigned and who received at least one dose of study treatment.

Safety Set

The **Safety Set** includes all patients who received at least one dose of any component of the study treatment.

Evaluable Set

The **Evaluable Set** consists of all evaluable patients in the FAS who have:

- centrally confirmed HGG through histology, and
- centrally confirmed positive BRAF V600 mutation, and
- an adequate tumor assessment at baseline, (An adequate tumor assessment at baseline refers to baseline measurable disease assessed by investigator and confirmed by central independent reviewer per RANO criteria), and

- either 1) a follow-up tumor assessment at week 8 day 1 visit or later (any assessment on or after day 43 allowing for the time-window around the visit) or 2) disease progression at any time or 3) have discontinued for any reason.

The evaluable set will be used for sensitivity analyses as defined in Section 2.5 and Section 2.7.

Patient Classification:

Patients may be excluded from the analysis populations defined above based on specific patient classification rules defined in Table 2-5 Patient classification rules for analysis sets Reasons leading to exclusion from analysis sets will be listed.

Table 2-5 Patient classification rules for analysis sets

Analysis set	Criteria leading to exclusion
FAS	No dose of study medication
Safety Set	No dose of study medication
Evaluable Set	Not centrally confirmed measurable disease at baseline, Not centrally confirmed HGG, Not centrally confirmed BRAF V600 mutant, Patients who do not have an adequate tumor assessment at baseline Patients who do not have a follow-up tumor assessment at least 43 days after starting treatment unless disease progression is observed before that time or patient discontinued for any reason.

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis data sets. The date on which a patient withdraws full consent is recorded in the eCRF.

Death events may be used in the analysis if captured from public records (registers), local law and subject informed consent permitting.

Additional data for which there is a separate informed consentcollected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroups of interest

Efficacy

No subgroup analyses of efficacy data are planned for the final CSR. [redacted]

Safety

Safety subgroup analyses will use the same method as for the analysis in the safety analysis set. Key safety analyses including:

- Overview of AEs
- AEs, regardless of relationship to study drug, by primary system organ class (SOC) and preferred term (PT)
- AEs related to the study drug, by primary SOC and PT
- Serious AEs, regardless of relationship to study drug, by primary SOC and PT

will be repeated on safety set in the following subgroups:

- Age group at enrollment (12 months- <6 years, 6 -< 12 years, 12 -< 18 years)
- Any prior antineoplastic chemotherapy (yes, no)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified.

For the final database lock, no analyses will be performed on basic demographic and background data, diagnosis and extent of cancer, medical history or other baseline data. As there have been no changes to patient enrollment since the primary analysis, the analyses performed for the primary analysis can be referred to for all baseline data.

2.3.1 Patient disposition

The number (%) of patients in the FAS who completed treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided: % based on the total number of FAS patients:

- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered);
- Number (%) of patients who completed the study treatment phase (based on the 'End of Treatment Disposition' page)
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Disposition' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Disposition' page);

- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post Treatment Phase Disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post Treatment Phase Disposition' page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Disposition' or 'End of Post Treatment Phase Disposition' page).
- Number (%) of patients who have rolled over to long-term follow-up study G2401. (based on the 'EOT_Rollover' disposition page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan). All protocol deviations will be listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized separately for dabrafenib and trametinib. The duration of exposure will also be presented for the study treatment of dabrafenib and trametinib combination therapy. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by dabrafenib and trametinib. The number (%) of patients with a dose re-escalation will also be summarized by treatment group.

Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to any combination partner.

Duration of exposure to study treatment (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the latest of the last dates of exposure to any combination partner (see Table 2-6 Definition of last date of exposure of study drug).

Summary of duration of exposure of study treatment in appropriate time units based on clinically meaningful time intervals (eg 8-<24, 24-<56, 56-<112, >= 112 (weeks)) will include categorical summaries and continuous summaries (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum) using appropriate units of time.

Duration of exposure to combination partner

Duration of exposure to a study drug (days) = (last date of exposure to investigational drug) – (date of first administration of investigational drug) + 1.

Table 2-6 Definition of last date of exposure of study drug

Definition of last date of exposure of study drug	Example
Date of last administration of a non -zero dose of the study drug.	A patient had a permanent discontinuation of the study drug 06Jan2013 after being put on a temporary interruption since 01Jan2013. In this case the last date of exposure is 31Dec2012.

Summary of duration of exposure to each combination partner will include categorical summaries based on clinically meaningful time intervals (8-<24, 24-<56, 56-<112, >= 112 (weeks)) and using descriptive statistics (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum) using appropriate units of time.

Cumulative dose and average daily dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study drug, respectively. Average daily dose is defined as [Cumulative dose (dosing unit) / Number of dosing days]; drug free days are not counted as dosing days.

Cumulative dose and average daily dose will be summarized both in mg and mg/kg. Total actual cumulative dose (mg/kg) of dabrafenib and trametinib is calculated as the sum of the daily doses in mg/kg, where the mg/kg dose on any particular day is calculated as the dose in mg divided by the current weight (collected as per the visit schedule). Total actual cumulative dose (mg) of dabrafenib and trametinib is calculated as the sum of the daily doses in mg.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of study drug administration. The planned dose (mg) will be taken from the planned dose (mg) times the frequency from the first dosing record. The planned cumulative dose will not be summarized/listed. It will be used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered over the duration for which the patient is on the study treatment as documented in the DAR eCRF page.

For patients who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

Dose intensity and relative dose intensity

Dose of dabrafenib and trametinib will be defined in the units of mg, and taken from the DAR eCRF.

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg/ day) = Actual Cumulative dose (mg) / Duration of exposure (day).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (mg/ day) = Planned Cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/ day) / PDI (mg/ day).

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components.

Summary of RDI will include categorical summaries based on clinically meaningful intervals (≤50%, >50-≤75%, >75-≤90%, >90-≤110%, >110%).

Table 2-7 Examples of dabrafenib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg) frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 05Jan2016	125 mg BID	250	No	No	
2	06Jan2016 / 03Feb2016	125 mg BID	200	Yes	No	AE
3	04Feb2016 / 25Feb2016	130 mg BID	260	Yes	No	As per protocol

Duration of exposure (days) = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 125*2*56 days = 14000 mg

Actual cumulative dose = 250*5 + 200*29 + 260*22 = 12770 mg

Dose intensity = 12770 mg / 56 days = 228.04 mg/day

Planned dose intensity = 14000 mg / 56 days = 250 mg/day

Relative dose intensity = DI / PDI = (228.04 mg/day) / (250 mg/day) = 91.2%

Table 2-8 Examples of trametinib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 10Jan2016	0.875 QD	0.875	No	No	
2	11Jan2016 / 15Jan2016	0.875 QD	0	Yes	No	AE

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
3	16Jan2016 / 25Feb2016	0.75 QD	0.75	No	No	AE

Duration of exposure = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 0.875*56 days = 49 mg

Actual cumulative dose = 0.875*10 + 0*5 + 0.75*41 = 39.5 mg

Dose intensity = 39.5 mg / 56 days = 0.705 mg/day

Planned dose intensity = 49 mg / 56 days = 0.875 mg/day

Relative dose intensity = DI / PDI = (0.705 mg/day) / (0.875 mg/day) = 80.6%

Dose reductions, interruptions, re-escalations or permanent discontinuations

The number of patients who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study drug. The number of patients who have dose re-escalations will also be summarized.

'Dose interrupted' and 'Dose permanently discontinued' fields from the Dosage Administration eCRF pages will be used to determine the dose interruptions and permanent discontinuations, respectively. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this block of entries, then it will be counted as one interruption.

Dose Reduction: Only dose change is collected in the eCRF, the number of reductions will therefore be derived programmatically based on the change and the direction of the change. A dose reduction is a dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Note that any dose change due to dispensing or dosing error will not be considered a dose reduction. Note also that any previous dose interruptions and any previous dosing or dispensing errors should be ignored when considering whether a subsequent dose change counts as a dose reduction, i.e., if the new dose is lower than the dose prior to any dose interruption or any dose or dispensing error this would still constitute a dose reduction. Missing data: If dose is recorded but regimen is missing or entered as 'none', it is assumed that the investigational drug was taken as per-protocol.

Dose Re-escalation: For patients with a dose reduction, a dose re-escalation is where the prescribed dose level is higher than the previous prescribed dose level or where the actual dose administered/total daily dose is higher than the calculated dose amount based on the prescribed dose. An increase will only be considered a dose re-escalation if the reason for dose change is "as per protocol". Note also that any previous dose interruptions and any previous dosing or dispensing errors should be ignored when considering whether a subsequent dose change counts as a dose re-escalation.

2.4.2 Prior, concomitant, on study and post therapies

Prior anti-cancer therapy

The analyses performed for the primary analysis can be referred to for details on prior anti-cancer therapies.

On-study radiotherapy and surgery

As on study radiotherapy is allowed after centrally confirmed radiologic progression of disease or at least a total of 36 months of treatment plus follow-up, whichever comes first, surgeries and radiotherapies occurring on study will be listed only.

For patients enrolled in the HGG cohort, anti-cancer surgery is allowed for patients enrolled on the study after at least 8 months on treatment or after radiologic progression of disease has been confirmed by investigator. Study treatment may be taken up to one day prior to surgery as deemed appropriate by the investigator.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, PT, and by means of frequency counts and percentages using FAS. In addition, listings will include best response to the regimen. Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD).

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the WHO Drug Reference Listing (DRL) dictionary that employs the ATC classification system and summarized by lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and

2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Non-drug therapies and procedures starting after the start of study treatment will also be summarized by SOC and PT.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Systemic corticosteroid use (flagged using a pre-specified list from the clinical team) will be listed and summarized by lowest ATC class and PT using frequency count and percentages. The total daily dose of systemic corticosteroids can be calculated from the dose per administration and the dose frequency (see Section 5.3). Any corticosteroid use starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

Concomitant medications that have the potential to impact some specific analyses (e.g. efficacy or safety analyses) will be identified prior to database lock. Separate summaries of these concomitant medications will be produced using the appropriate analysis set (e.g. FAS for those potentially affecting efficacy. According to the study protocol, treatment with substances which are strong inhibitors, or inducers of CYP3A4/5 and CYP2C8, or antiretrovirals or herbal medicines or other anti-cancer or anti-investigational drugs should be avoided. However, some patients may take these substances during the treatment period so these concomitant medications will be selected via programming and tabulated and listed in the CSR. Treatment with the prohibited substances mentioned above will be identified in the database as protocol deviations.

2.5 Analysis of the primary objective

The primary objective is to demonstrate the antitumor activity of dabrafenib in combination with trametinib as measured by ORR to study treatment by central independent review assessment using RANO criteria, in children and adolescent patients with BRAF V600 mutation positive relapsed or refractory HGG.

2.5.1 Primary endpoint

ORR is defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) according to RANO criteria (see Appendix 3 of the study protocol). ORR will be calculated based on the FAS using central independent review of tumor assessment data. Only tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. See Section 5.6 for primary estimand definition.

Best overall response

The BOR will be assessed based on reported responses across all evaluation time points. Both CR and PR must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met. The next scheduled assessment may be used for purposes of

confirmation of response. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease (SD).

BOR for each patient is determined from the sequence of overall responses according to the following rules, up to progression:

- CR = at least two determinations of CR at least 4 weeks apart before progression
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
- SD = requires at least one SD assessment (or better) determined at or beyond the second regularly scheduled tumor assessment (nominally week 16 i.e >= 105 days allowing for the ±1 week visit window) after start of study treatment (and not qualifying for CR or PR).
- PD = progression after start of study treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD at or beyond the second regularly scheduled post-baseline tumor assessment or progression)

If a patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the BOR determination. Further anti-neoplastic therapies will be identified via protocol deviations or from the data collected on 'Anti-neoplastic therapies since last date of study drug' as appropriate.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed on the FAS. Point estimate and two-sided exact binomial exact 95% and 80% confidence intervals (CIs) [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413] of ORR will be provided. The analysis performed at the time of final analysis will only be considered descriptive and therefore no hypothesis test will be performed. Handling of missing values/censoring/discontinuations

Patients with unknown or missing BOR will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the BOR must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'failures'.

2.5.3 Supportive analyses

As sensitivity analysis, ORR will be calculated and summarized for patients from the Evaluable Set. ORR will be summarized using descriptive statistics (N, %) along with two-sided exact binomial 95% and 80% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

New anticancer therapy sensitivity analysis for ORR

The analyses of ORR will be repeated using a stricter ITT approach i.e. including all response assessments irrespective of new anti-neoplastic therapy using the FAS. This analysis will only be performed if data permits.

Response evaluations recorded after the initiation of new anti-neoplastic therapy will be included in sensitivity analysis of ORR, (i.e. the occurrence of new anti-neoplastic therapy will be ignored for the analyses). The sensitivity analyses will be performed based on both the investigator and independent review assessments using the FAS. In the summary tables, this approach is referred as 'new anticancer therapy ORR sensitivity analysis'.

Concordance analysis of ORR

An assessment of the concordance between central independent reviewer assessment and local investigator assessment of the BOR for each patient will be provided. The calculation will be based on the percent agreement (the proportion of response outcomes that agree or match across both independent reviewer and investigator assessments).

Reasons for "Unknown" BOR

Patients with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD and/or unconfirmed CR/PR only occurring prior to week 16 visit

2.6 Analysis of the key secondary objective

Not Applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are to:

- Evaluate ORR by investigator assessment per RANO
- Evaluate duration of response (DOR) by investigator and central independent review per RANO
- Evaluate progression-free (PFS) survival by investigators and central independent review assessment per RANO
- Evaluate time to response (TTR) by investigators and central independent review assessment per RANO
- Evaluate CBR by investigators and central independent review assessment per RANO
- Evaluate overall survival (OS)

2.7.1 Secondary endpoints

ORR by investigator assessment

The evaluation of ORR will be repeated by investigator assessment as per RANO criteria based on the FAS and the Evaluable Set separately. ORR will be summarized using descriptive statistics (N, %) along with 2-sided exact 95% and 80% CIs [Clopper CJ and Pearson ES. (1934)

The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

Duration of response

DOR only applies to patients whose BOR is CR or PR according to RANO criteria. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression per RANO or death due to any cause. If a patient has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, DOR will be censored at the date of the last adequate tumor evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier (see Section 2.7.3).

DOR will be analyzed as per investigator and central independent review separately. The analyses of DOR will be based on the FAS and will be repeated based on the evaluable set.

Progression-free survival

PFS is defined as the time from the start date of study treatment to the date of the first documented progression or death due to any cause. PFS will be calculated using RANO criteria based on investigator and central independent review of tumor assessments separately. The analysis will include all data observed up-to the cut-off date. If a patient has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier. (See Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment). Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages) without supporting evidence satisfying progression criteria per RANO will not be considered disease progression for PFS derivation. The analysis will be based on FAS and Evaluable Set separately.

Time to response

Time to response (TTR) of CR or PR is the time from start date of study treatment to first documented response of CR or PR (which must be confirmed subsequently) according to RANO criteria. All patients in the FAS will be included in the TTR calculation. Patients who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FPFV - LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other patients.

TTR will be analyzed using investigator and independent reviewer assessments separately.

Clinical Benefit Rate

CBR is defined as the proportion of patients with a BOR of CR or PR, or an overall lesion response of SD which lasts for a minimum duration of 24 weeks. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 23 weeks or later (i.e. $\geq$ 161 days) from treatment start date, allowing for the $\pm$1 week visit window for tumor assessments.

CBR will be analyzed using investigator and independent reviewer assessments separately. CBR will be calculated using the FAS set and Evaluable Set separately.

Overall Survival

OS is defined as the time from start date of study treatment to date of death due to any cause.

If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact (Section 2.1.1) .

2.7.2 Statistical hypothesis, model, and method of analysis

ORR by investigator assessment

ORR assessed by investigator assessment per RANO criteria will be summarized using descriptive statistics (n, %) along with two-sided exact binomial 95% CIs and 80% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

All response data will be listed by investigator and central independent review assessment.

Time to response

TTR data will be listed and summarized. The distribution of TTR will be estimated using the Kaplan-Meier method and the median TTR will be presented along with 95% CI only if a sufficient number of responses is observed. In addition, a responders-only analysis will also be performed in this case using descriptive summary statistics.

Duration of response

DOR will be listed and summarized for all patients with confirmed BOR of CR or PR. The Kaplan-Meier estimate of the distribution function will be constructed and the number of patients at risk at certain time points will be shown on the plot. The estimated median (in weeks) along with 95% CIs, as well as 25th and 75th percentiles will be reported [Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-22.

Brookmeyer R and Crowley J. (1982)]. In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs [Kalbfleisch JD and Prentice RL. (2002)] at several time points (including at least 4, 6, and 12 months) will be summarized. Censoring reasons will also be summarized.

Progression-Free Survival

PFS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at 6, 12, 18 and 24 months. Censoring reasons will also be summarized.

Clinical Benefit Rate

CBR will be summarized using descriptive statistics (n, %) along with two-sided exact binomial 95% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

Overall Survival

OS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR, including estimated median (in months) with 95% CI [Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-22.

Brookmeyer R and Crowley J. (1982)], 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at timepoints up to the maximum follow-up (including at least 6, 12, 18 and 24 months).

2.7.3 Handling of missing values/censoring/discontinuations

DOR and PFS

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy, DOR and PFS will be censored at the date of the last adequate tumor before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the start date of treatment will be used.

In particular, DOR and PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is administered; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-9 for censoring and event date options and outcomes for DOR and PFS.

Table 2-9 Outcome and event/censor dates for DOR and PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of start of study treatment	Censored
Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed

Situation	Date	Outcome
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
New anticancer therapy (including cancer related surgery and radiotherapy) given prior to protocol defined progression	Date of last adequate assessment on or prior to starting new anti-cancer therapy	Censored
Death before first PD assessment	Date of death	PFS event

Censoring pattern of PFS

Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Initiation of new cancer therapy prior to progression
6: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments (see Section 2.7.3 for definition):

1. Analysis cut-off date,
2. Start date of further anti-neoplastic therapy,
3. Date of consent withdrawal,
4. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. ‘Ongoing’,
2. ‘New cancer therapy added’,
3. ‘Withdrew consent’,
4. ‘Lost to follow-up’,

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed. then the PFS censoring reason will always default to ‘Adequate assessment no longer available’. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than the interval of 2 missing tumor assessments then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced for PFS by investigator and central independent reviewers. The censoring patterns will be compared between investigator and central independent reviewers.

OS

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date patient was alive, i.e., last contact date (see Section 2.1.1).

2.7.4 Supportive analyses

ORR, DOR, and PFS based on radiographic response by independent review assessment

The analyses of ORR, DOR, and PFS will be repeated based on radiographic response assessed by independent review by only incorporating the radiographic data which includes the lesion measurements from target lesions, non-target lesions, and new lesion per RANO. Clinical status data and corticosteroid use data will not be considered for the supportive analyses based on radiographic response. Waterfall plot will be presented for this analysis.

Waterfall graphs will be used to depict the anti-tumor activity for independent and investigator assessments.. These plots will display the best percentage change from baseline in the sum of the products of perpendicular diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall graphs. Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. A patient with only such assessments will be represented by a special symbol (e.g. ✶) in the waterfall graph. Assessments with "unknown" target lesion response and assessments with unknown overall response will be denoted in the waterfall plots. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of patients with tumor shrinkage and tumor growth. Bars will have different fill patterns for all possible values of overall response. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-10.

Table 2-10 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
case	Target response	Overall lesion response	Include in waterfall?	Non-target response	New lesion?
1	CR/PR/SD	PD	Yes as a bar	PD	any
2	CR/PR/SD	PD	Yes as a bar	any	Yes
3	UNK	UNK or PD	Yes as an x	any	any
4	CR/PR/SD	UNK	Yes as a bar	UNK	No

5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
6	PD	PD	Yes as a bar	any	any

Additionally, swimmer plots of time to onset and DOR based on independent and investigator review will be created for the FAS.

Corticosteroids use

The drug name, dose, reason, dosing frequency per interval, and dose intensity will be listed. The dose intensity is calculated as the cumulative dose divided by the duration of exposure per interval. Any corticosteroids use starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

New anticancer therapy sensitivity analysis for DOR and PFS

Response evaluations and events (i.e. RANO. documented disease progression or death) recorded after the initiation of new anti-neoplastic therapy will be included in sensitivity analyses of DOR and PFS, (i.e. the occurrence of new anti-neoplastic therapy will be ignored for the analyses). The sensitivity analyses will be performed based on both the investigator and independent review assessments using the FAS and using the same statistical methods for DOR and PFS described in Section 2.7.2. In the summary tables, this approach is referred as 'new anticancer therapy DOR sensitivity analysis' and 'new anticancer therapy PFS sensitivity analysis'.

2.8 Safety analyses

All safety analyses will be based on the safety set unless otherwise specified.

2.8.1 Adverse events (AEs)

AEs are coded using MedDRA terminology. The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary SOC and for each PT using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PT will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency.

The following AE summaries will be produced: overview of AEs and deaths (number and % of subjects who died, with any AE, any serious adverse event (SAE), any dose reductions/interruptions etc.), AEs by SOC and PT, summarized by relationship to study treatment (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, and leading to fatal outcome. In addition, a summary of serious and non-serious AEs with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same PT) as per EudraCT requirements.

For legal requirements of clinicaltrials.gov and EudraCT, two required tables for on-treatment AEs which are not SAE's with an incidence greater than and equal to 5% and on-treatment SAE's and SAE's suspected to be related to study treatment will be provided by SOC and PT on the safety set population

2.8.1.1 Adverse events of special interest / grouping of AEs

All AE groupings for a clinical program are stored in the electronic Case Retrieval Strategy (eCRS) with clear versioning and reference to the MedDRA version used.

All adverse events of special interest (AESI) definitions or AE grouping need to be specified in the eCRS. If an eCRS update is necessary, the final version needs to be available before the final database lock. The eCRS version should be included in a footnote of the AESI tables.

Data analysis of AESIs

An AESI is a grouping of AEs that are of scientific and medical concern specific to dabrafenib and trametinib. These groupings are defined using MedDRA terms, standardized MedDRA queries (SMQ), high-level group terms, high-level terms) and PT. Customized Novartis MedDRA queries (NMQ) may also be used. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on-treatment period will be summarized. Any AESI categories with zero events will also be displayed in the summary tables.

AESI for dabrafenib and trametinib are:

- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Hypertension

- Pyrexia
- Pre-Renal and intrinsic renal failure
- Uveitis
- New primary /secondary malignancy
- Hypersensitivity
- Hyperglycemia
- Venous thromboembolism
- Pancreatitis
- Neutropenia

Summaries of these AESIs will be provided by dabrafenib and trametinib, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment / interruption, fatal outcome, etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths including on-treatment and post-treatment deaths will be produced by SOC and PT.

All deaths will be listed for the Safety set, post-treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.8.3 Laboratory data

Data handling

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Data analysis

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of lab parameter values for serum creatinine over time (baseline and selected on-treatment time points) will be displayed via boxplots based on time windows for patients with values at baseline and 6 months or greater and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

Potential Hy's Law events are defined as those patients with occurrence of AST or ALT > 3xULN and TBL > 2xULN and missing ALP or ALP < 2xULN at any time during the on-treatment period . Note that the criteria relating to combined elevations of AST (or ALT) and TBL are based on the peak values at any post-baseline time for a subject.

For patients with abnormal ALT or AST baseline values, a clinically significant liver safety signal corresponding to Hy's law is defined by : [ALT or AST > 3xbaseline] OR [ALT or AST >8xULN], whichever is lower, combined with [TBIL >2xbaseline AND >2*ULN]A figure displaying time course of hepatic function tests (ALT, AST, TBL, ALP) in patients meeting Hy's criteria will be displayed in the Safety Set. Additonally, evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be produced to display ALT and AST values by TBL values in units of ULN.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

ECG Data analysis

Standard 12-lead ECGs including PR, QRS, QT, QTcF, and HR intervals will be obtained local for each patient during the study. ECG data will be read and interpreted locally.

The number and percentage of patients with notable ECG values will be presented:

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

The normal range for HR is displayed in Table 2-11 Recommendation for normal heart rate per age group and gender. The number and percentage of patients with notable values will be presented.

Table 2-11 Recommendation for normal heart rate per age group and gender

Age group	1-<3 years	3-<5 years	5-<8 years	8-<12 years	12-<16 years	16-<20 years	20-<30 years
HR (bpm) Boys	(95, 155)	(75, 125)	(60, 115)	(55, 100)	(50, 100)	(50, 105)	(45, 95)
HR (bpm) Girls	(95, 180)	(80, 125)	(70, 115)	(60, 110)	(50, 100)	(45, 105)	(50, 100)

Age should be age at assessment. Data shown as upper limit of normal, lower limit of normal for HR= heart rate. Ref.: adapted from Rijnbeek et al. 2001 and Rijnbeek et al. 2014

The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. A listing of all ECG assessments will be produced and notable values will be flagged. A separate listing of only the patients with notable ECG values may also be produced. In the listings, the assessments collected during the post-treatment period will be flagged.

The denominator to calculate percentages for each category is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline ECG notable value is defined as a post-baseline value that meets the criterion post-baseline but did not meet the criterion at baseline.

For each ECG parameter, descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized. Descriptive statistics at worst post-baseline and changes from baseline to worst post-baseline will also be summarized separately.

For each of the QTc and QT intervals, shift tables based on notable parameter categories (<450, 450-<481, 481-<501, ≥501 ms) at baseline and the worst post-baseline value observed.

Frequency counts and percentages of patients with newly occurring post-baseline qualitative ECG abnormalities (morphology) will be summarized. The denominator to calculate percentages is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline qualitative ECG abnormality is defined as a post-baseline abnormal finding which was not present at baseline.

Patients with notable ECG interval values and newly occurring qualitative ECG abnormalities will be listed and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

ECHO Data handling

ECHO data will be analyzed based on local reported results. The summaries will include all ECHO assessments performed no later than 30 days after the last date of study drug. All ECHO assessments will be listed, and those collected later than 30 days after study drug discontinuation will be flagged in the listing.

The same modality (ECHO or MUGA) for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) should be used to follow a patient throughout the study. The absolute change from baseline values will not be calculated for any patients where the post-baseline value was determined by a cardiac scan modality that is different than the one used to determine baseline value.

ECHO Data analysis

Absolute change from baseline in LVEF will be summarized in the worst case post-baseline. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- No change or any increase
- Any decrease:
  - > 0 - <10% Decrease
  - 10 - <20% Decrease
  - ≥20% Decrease
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

ECHO assessments of LVEF will be listed for each patient including absolute change from baseline at each assessed time interval. The values of potential clinical importance will also be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters are being collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on-treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-12 Criteria for notably abnormal vital signs below.

Table 2-12 Criteria for notably abnormal vital signs

	Clinically notable criteria	
Vital sign (unit)	High	Low
Systolic blood pressure [mmHg]	≥ 95th percentile of the age and height group[1]	≤ 5th percentile of the age and height group[1]

	Clinically notable criteria			
Vital sign (unit)	High		Low	
Diastolic blood pressure [mmHg]	≥ 95th percentile of the age and height group[1]		≤ 5th percentile of the age and height group[1]	
Body temperature [°C]	≥ 38.4°C		≤ 35.0°C	
Pulse rate [bpm][2]	12-18 months	> 140	12-18 months	< 103
	18-24 months	> 135	18-24 months	< 98
	2-3 years	> 128	2-3 years	< 92
	3-4 years	> 123	3-4 years	< 86
	4-6 years	> 117	4-6 years	< 81
	6-8 years	> 111	6-8 years	< 74
	8-12 years	> 103	8-12 years	< 67
	12-15 years	> 96	12-15 years	< 62
	≥ 15 years	> 92	≥ 15 years	< 58
Weight	increase from baseline of ≥ 2 BMI-for-age percentile categories[3]		decrease from baseline of ≥ 2 BMI-for-age percentile categories[3]	

bpm=beats per minute; CDC= Centers for Disease Controls and prevention; NHLBI= National Heart, Lung, and Blood Institute;

[1] Blood pressure percentiles are calculated for each blood BP record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; 377: 1011-18.

[3] BMI-for-age percentiles categories (P3, P5, P15, P25, P50, P75, P85, P95, P97) are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/);

Note: For patients less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the recumbent length; for patients over 228 months- old, percentiles are not available and will be considered as missing.

The number and percentage of patients with notable vital sign values (high/low) will be presented.

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP. Baseline is defined as the last non-missing value prior to or coinciding with first dose. The worst post-baseline value refers to the worst post-baseline value on treatment.

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure. For each parameter, only patients with a value at both baseline and post baseline (on treatment) will be included. For pulse parameter, the subject can be counted in both low and high categories and with a subject contributing to multiple age categories as data is collected over time.

A listing of all vital sign assessments will be produced by and notable values will be flagged. A separate listing of only the patients with notable vital sign values may also be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Performance status

The Karnofsky and Lansky performance status scale (Table 2-13 Performance status criteria) will be used to assess physical health of patients.

Table 2-13 Performance status criteria

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be in multiples of 10			
Karnofsky (age >16 years of age)		**Lansky** (age <16 years)	
Score	**Description**	**Score**	**Description**
100	Normal, no complaints no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity, minor signs of symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort, some signs of symptoms of disease.	80	Active, but tires quickly.
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play, keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.

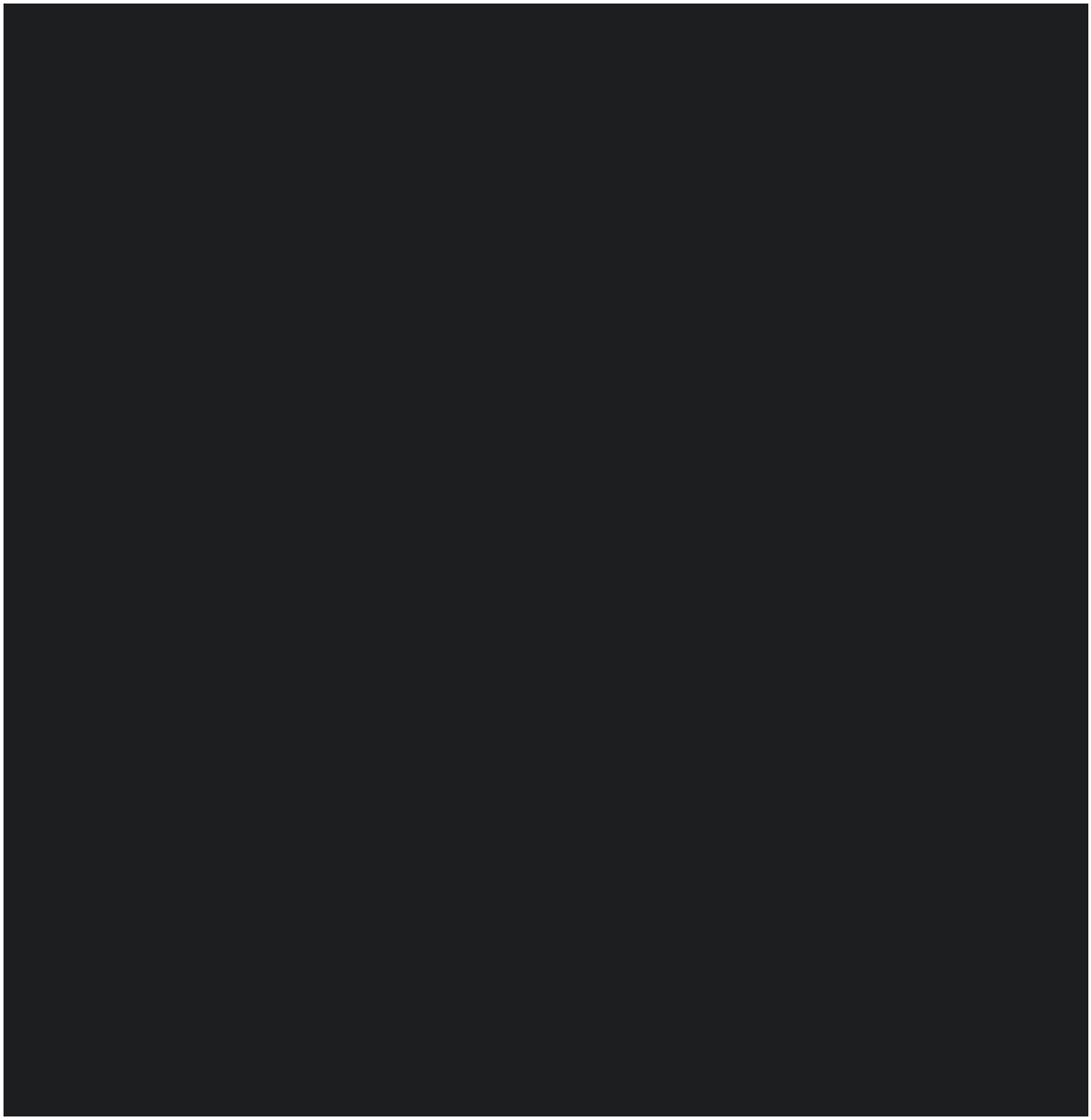
Frequency counts and percentages of patients in the score category of 100, 90, 80, 70, and < 70 will be provided by time point based on the windows defined in Section 2.1.1. A summary of change from baseline by scheduled visits will be performed, as well as the worst case post-baseline (lowest value during the on-treatment period) and the best case post-baseline (highest value during on-treatment period) changes during the study.

A supporting listing will also be provided.

2.8.4.4 Dermatological Evaluation

Skin examination results will be summarized by frequency counts and percentages of patients in each category (normal, abnormal) by scheduled time points. A supporting listing will also be provided.

[redacted]



2.8.4.7 Growth and development (Height and Weight)

Growth data consist of height, BMI, height SDS, BMI SDS, height velocity SDS, weight velocity SDS, height velocity and weight velocity.

Height and weight will be summarized at 6-month intervals during the on-treatment period, using the standard deviation scores (SDS, also called Z-score), velocity and velocity SDS. The relevant height and weight values for each 6-month period are defined using time windows, as defined in Table 5-4. The Z-scores will allow identification of potential outliers.

The formula used to calculate the SDS and height and weight velocities are provided in the Appendix 5.4.2.

Note that BMI SDS are reported instead of weight SDS as no reference data for weight are provided by the WHO for age beyond 10.

Height and BMI SDS and height and weight velocity SDS will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, minimum, maximum) for each time window (at baseline and thereafter allowing informal comparison of growth data), as well as by presenting number of patients with SDS values lower/higher than $5^{th}/95^{th}$ percentiles respectively.

Box plots will be plotted for each time window. A shift table to compare baseline SDS to the worst on-treatment SDS categorized as Low (SDS < -1.645), High (SDS > 1.645) or Normal (-1.645 ≤ SDS ≤ 1.645) will be produced for height and BMI SDS. Another shift table to compare the baseline height SDS to the last available on-treatment height SDS categorized according to the main percentile lines (>95^{th}, 95^{th} to 90^{th}, 90^{th} to 75^{th}, 75^{th} to 50^{th}, 50^{th} to 25^{th}, 25^{th} to 10^{th}, 10^{th} to 5^{th} and ≤5^{th} percentile) will be produced.

2.8.4.8 Ophthalmologic exam

Visual acuity will be converted from snellen to logMAR scale as defined in [Holladay 1997 (20)], and categorized as the following change from baseline:

- Improvement: ≥ 0.2 logMAR improvement (decrease in logMAR)
- Stable: neither ≥ 0.2 logMAR improvement nor worsening, where
- Worsening: ≥ 0.2 logMAR worsening (increase in logMAR)

Visual acuity categories at each time point, as well as best and worst category on treatment will be presented. [redacted]

2.8.4.9 Palatability

Data on palatability were analyzed at the time of primary analysis and no further data have been collected. The analysis of palatability data will not be repeated at the final analysis.

2.8.4.10 Additional analyses

Time to first occurrence

Time to first occurrence of an event is defined as time from start of study treatment to the date of first occurrence of this event (or first event within an AE grouping), i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.

For Kaplan-Meier analyses of time to occurrence, in the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- end date of on-treatment period

- data cut-off date
- withdrawal of informed consent date.

Failure curves (ascending Kaplan-Meier curves) will be constructed. Median together with 95% CI as well as 25th percentile and 75th percentile will be presented.

In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

2.9 Pharmacokinetic endpoints

Pharmacokinetic (PK) analyses were performed at the time of primary analysis and no further data have been collected. The analysis of PK data will not be repeated at the final analysis.

2.10 Patient-reported outcomes

Not applicable.

3 Sample size calculation

The sample size calculation was based on the primary analysis and is not applicable for the final analysis.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of date of last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EoT eCRF page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EoT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EoT visit date is complete, then this latter date should be used.

Case 2: Only Year (yyyy) of the dose end date is available and yyyy < the year of EoT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EoT date:

Use EoT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EoT date and mm < the month of EoT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of that specific record, if the imputed date is < start date of that record:

Use the start date of that record

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2 AE, concomitant medications and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and concomitant medications with partial/missing dates will be displayed as such in the data listings.

Any AEs and concomitant medications which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications, and for assigning pre/on/post treatment periods.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is

progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

AEs are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the CTCAE version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Systemic corticosteroids

Systemic corticosteroids should be flagged based on a list provided by the clinical team. Further details will be provided in the programming datasets specifications (PDS).

The total daily dose can be calculated by multiplying the dose per administration by the factor specified in Table 5-3 according to the specified dosing frequency.

Table 5-3 Multiplicative factors to calculate total daily dose

Frequency	Meaning	Multiply dose per administration
BID	Twice per day	2
BIW	Twice per week	0.2857
Continuous	-	*Set to missing*
Daily	Once per day	1
Once	-	1
Other	-	*Set to missing*
PRN	As required	*Set to missing*
QD	Once per day	1
QH	Once per hour	24
Q2H	Once every 2 hours	12
Q3H	Once every 3 hours	8
Q4H	Once every 4 hours	6
Q5H	Once every 5 hours	4.8
Q6H	Once every 6 hours	4

Frequency	Meaning	Multiply dose per administration
Q8H	Once every 8 hours	3
Q12H	Once every 12 hours	2
Q14H	Once every 14 hours	1.7143
Q18H	Once every 18 hours	1.3333
Q24H	Once every 24 hours	1
QID	Four times per day	4
QM	Once per month	0.0328
Q2M	Once every 2 months	0.0164
Q3M	Once every 3 months	0.0110
QOD	Once every other day	0.5
QW	Once per week	0.1429
Q2W	Once every 2 weeks	0.0714
Q3W	Once every 3 weeks	0.0476
Q4W	Once every 4 weeks	0.0357
TID	Three times per day	3
TIW	Three times per week	0.4286
Unknown	-	*Set to missing*
Weekly	Once per week	0.1429
5x per day	Five times per day	5
6x per day	Six times per day	6
7x per day	Seven times per day	7
8x per day	Eight times per day	8

5.4 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of white blood cells (WBC).

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.4.1 Growth data

SDS will be calculated using the current formulae provided by the WHO as follows:

1. Calculate $z_{ind} = \frac{\left(\frac{X}{M}\right)^{L} - 1}{LS}$
2. If $|z_{ind}| \leq 3$, SDS = z_{ind}
   If $z_{ind} > 3$, SDS = 3 + (X – SD3*pos*) / SD23*pos*
   If $z_{ind} < -3$, SDS = -3 + (X – SD3*neg*) / SD23*neg*

where:

- *X* is height in centimeters or BMI in kilograms/m^2,
- *L*, *M* and *S* are height or BMI-, sex- and age-specific reference values from the WHO Growth Charts.
- SD3*pos* is the cutoff 3SD calculated by the LMS method:
  SD3*pos* = M * (1 + LS*3)$^{1/L}$
- SD3*neg* is the cutoff -3SD calculated by the LMS method:
  SD3*neg* = M * (1 + LS*(-3))$^{1/L}$
- SD23*pos* is the difference between the cutoffs 3SD and 2SD:
  SD23*pos* = M * (1 + LS*3)$^{1/L}$ - M * (1 + LS*2)$^{1/L}$
- SD23*neg* is the difference between the cutoffs -2SD and -3SD:
  SD23*neg* = M * (1 + LS*(-2))$^{1/L}$ - M * (1 + LS*(-3))$^{1/L}$

Height-for-age and BMI-for-age L, M and S reference values for males and females are available under [http://www.who.int/childgrowth/standards/en/] (for patients aged between 0 to 5 years old) and [http://www.who.int/growthref/en/] (for patients aged between 5 to 19 years old). Note: use age in months at time of assessment "(visit date – date of birth) / 30.4375" rounded to the nearest whole month for corresponding values of L, M and S. These correspond to the latest available international references available at this time and described in the 2007 Bulletin of the WHO [Mercedes de Onis et al 2007]. SDS is actually a Z score that measures the distance from the population mean in units of standard deviations. That is, SDS < 0 refers

to values lower than the population mean, and for example SDS ≤ -1.645 refers to values in the lowest 5%.

The SDS score can be converted to a percentile assuming a standard normal distribution [mean=0, standard deviation =1]. Note that BMI is reported instead of weight as no reference data are provided by the WHO for age beyond 10.

Height velocity is defined as follows:

Height velocity (cm/6-months) = (height in time window *k* – height in time window *k-1*) ÷ ([assessment date in time window *k* – assessment date in time window *k-1*] ÷ [365.25/2]), and similarly for weight velocity.

Velocity SDS is calculated as (velocity – mean) / standard deviation, where mean and standard deviation are obtained as the height-, weight-, sex- and age-specific values [Baumgartner et al 1986], where the age category immediately above the patient's exact age (at the assessment date in time window *k*) should be used. Velocity SDS will only be calculated for time window *k* if data also exists for time window *k-1*, since calculating across multiple units of 6 months requires more than one reference value to be taken into account.

Table 5-4 summarizes the time windows for growth data, where windows are centered at every 6 months after start of study treatment. Although height and weight are collected more frequently than every 6 months (post-enrollment), this choice of time window length was made to reflect the degree of accuracy in the reference values (every 6 months) that will be used in the calculation of summary variables of growth.

In case of multiple assessments falling into the time window interval, the closest to the target date will be considered. For example, If there are three assessments falling under the time window of Day 85 to 252, then the closest one to target day of 168 will be considered. If two assessments are equidistant from target date, the average will be considered of those respective assessments.

Table 5-4 Time windows for growth data (height SDS, height velocity, weight velocity, BMI SDS)

Planned assessment	Time window
Baseline	Days ≤1
Month 6 (Day 168)	Days 85 – 252
Month 12 (Day 336)	Days 253 – 420
Month 18 (Day 504)	Days 421 – 588
Month xx (Day xx * 28)	Days ((xx – 3) * 28 + 1) – Day ((xx + 3) * 28)
End of treatment (EoT)	Earliest data available on or after EoT date up to and including 30 days after EoT

Day 1 = date of first intake of study drug
xx = Every 6 months

5.4.2 Bone Age

Bone age SDS will be calculated as (bone age – chronological age) / standard deviation) where the chronological age is the age in months at the time of the X-ray evaluation and the standard deviation is the sex- and age-specific standard deviation, as defined in the table below:

Table 5-5 Variability in Bone Age

Chronologic Age in Months	Boys Standard Deviation	Girls Standard Deviation
12	2.1	2.7
18	2.7	3.4
24	4	4
30	5.4	4.8
36	6	5.6
42	6.6	5.5
48	7	7.2
54	7.8	8
60	8.4	8.6
66	9.1	8.9
72	9.3	9
84	10.1	8.3
96	10.8	8.8
108	11	9.3
120	11.4	10.8
132	10.5	12.3
144	10.4	14
156	11.1	14.6
168	12	12.6
180	14	11.2
192	15	15
204	15.4	15.4

If the chronologic age falls between two values in the table above, the closest age should be used. If the chronologic age falls exactly in the middle between 2 values in the table above, then the age above the chronologic age should be used.

Table 5-6 Time windows for bone data

Planned assessment	Time window
Baseline	Days ≤1
Month 6 (Day 168)	Days 85 – 252
Month 12 (Day 336)	Days 253 – 420
Month 18 (Day 504)	Days 421 – 588
Month xx (Day xx * 28)	Days ((xx – 3) * 28 + 1) – Day ((xx + 3) * 28)
End of Treatment (EoT)	Earliest data available on or after EoT date up to and including 30 days after EoT

Day 1 = date of first intake of study drug
xx = Every 12 months

5.5 Statistical models

5.5.1 Primary analysis

Responses will be summarized in terms of percentage rates with 95% and 80% CIs. An exact binomial CI (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI.

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used by changing **level** = "No". From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$LCL_{LEVEL="Yes"}\ (\%) = 100\% - UCL_{LEVEL="No"}\ (\%)$$

$$UCL_{LEVEL="Yes"}\ (\%) = 100\% - LCL_{LEVEL="No"}\ (\%)$$

Multiplicity adjustment

Not applicable.

5.5.2 Key secondary analysis

Not applicable.

5.5.3 Secondary efficacy analysis

To analyze time to event endpoints (TTR, DOR, PFS and OS). An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. The TIME statement will include a variable with survival times and a (right) censoring variable with a value of 1, representing censoring. Kaplan-Meier survival and failure function estimates from this procedure will be used to construct the Kaplan-Meier figures.

Median survival will be obtained along with 95% CI calculated from PROC LIFETEST output using the method of [Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-22.

Brookmeyer R and Crowley J. (1982)]. Kaplan-Meier estimates of the survival function with 95% CI at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collet D (1994).].

5.5.4 Implementation of RANO guidelines (protocol Appendix 3)

As described in the protocol, the ORR will be evaluated by RANO criteria for solid tumors. This section provides some details on how to derive these endpoints by RANO and further details are included in the protocol Appendix 3.

The RANO criteria for assessment of LGG differs from that for HGG primarily in that LGG assessments utilize T2/FLAIR imaging while HGG assessments utilize Gadolinium enhanced imaging.

The major differences between RECIST 1.1 and RANO include:

- The measurability criteria for target lesion by RANO is based on two dimensions i.e two perpendicular diameters are measured for each target lesion;
- Corticosteroids use and clinical status are also considered for determining overall response;
- There are two types of non-target lesions by RANO: T1 enhancing non-target lesions and lesions on T2/FLAIR. Both types of non-target lesions contribute to the non-target lesion response.

Overall Lesion Response Collected on RANO eCRF page

In this study, Independent reviewer reported overall response and Investigator reported overall lesion response will be used for primary and secondary endpoints.For investigator, the overall response by RANO will be derived based on the collected overall lesion response on eCRF page "RANO Overall Lesion Response" (ZR domain, ZRCAT = "RESPONSE ASSESSMENT IN NEURO-ONCOLOGY", and ZRSCAT = "OVERALL LESION RESPONSE").

For independent reviewer, the overall response by RANO will be derived based on the collected overall lesion response on eCRF page "RANO Overall Lesion Response" (ZR domain, ZRCAT = "RESPONSE ASSESSMENT IN NEURO-ONCOLOGY", and ZRSCAT = "OVERALL RESPONSE").

There will be two evaluations at a given assessment for independent reviewer i.e. primary RANO radiologic review without clinical data (read 1 – ZREVAL = "PRIMARY REVIEW") and a secondary RANO review with clinical data (read 2 – ZREVAL = "SECONDARY REVIEW"). Secondary RANO review (read 2) with clinical data will be used for the primary endpoint of Best overall response per independent review. Primary review (read 1) will be used in supportive analyses based on radiographic review only, without clinical data.

Calculation of Overall Lesion Response by RANO

Overall lesion responses by RANO are also calculated from the following components:

1. Target lesion measurements;
2. Non-target lesion response;
3. New lesion present (Yes/No);
4. Corticosteroids use;
5. Clinical status.

All these components are collected on the following eCRF pages for investigator:

1. RANO target lesion - Measurable enhancing lesion (T1) (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”TARGET ENHANCING T1”);
2. RANO non-target lesion - Non-measurable enhancing lesion (T1) (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”NON-TARGET ENHANCING T1”);
3. RANO non-target lesion - Non-enhancing lesion (T2/FLAIR) (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”NON-TARGET NON ENHANCING T2/FLAIR”);
4. RANO New Lesion (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”NEW”);
5. Corticosteroids use and clinical status are collected on the Modified RANO Assessment (ZR domain, ZRCAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”RESPONSE ASSESSMENT”).

All the above components are collected on the same eCRF pages for independent reviewer with the exception of ZICAT = ” RESPONSE ASSESSMENT IN NEURO-ONCOLOGY”.

Each target lesion by RANO criteria has two perpendicular diameters collected. In order to calculate the target lesion response, the product of the two perpendicular diameters is calculated for each target lesion. Then the sum of the products of diameters of all target lesions is compared to the baseline or nadir to determine the target lesion response.

The non-target lesion response is collected on the field of “Non-target lesion present” in the Modified RANO Assessment page, and is evaluated based on both non-target lesion eCRF pages as shown above.

The RANO response/progression criteria are summarized in Table 5-7.

Table 5-7 Summary of the RANO response criteria

	CR	PR	SD	PD
T1-enhancing disease	None	≥50% decrease from baseline	<50% decrease from baseline but <25% increase from nadir	≥25% increase from nadir*
T2/FLAIR	Stable or improved	Stable or improved	Stable or improved	Unequivocal PD*
New Lesions	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA**
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Worsened*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease
*: Progression occurs when this criterion is met
**: Not Applicable (NA): Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

5.6 Estimands

5.6.1 Primary estimand for the primary objective

The primary clinical question of interest is: what is the ORR by independent review as per RANO criteria for the combination treatment of dabrafenib + trametinib in children and adolescent subjects with BRAFV600 mutant relapsed or refractory HGG, regardless of study treatment discontinuation and before start of any new anti-neoplastic therapy.

The justification for the primary estimand is that it will capture the treatment effect of the study drug even after treatment is discontinued, but avoid potential confounding effects of any other new anti-neoplastic therapy.

The primary estimand is characterized by the following attributes:

1. Population: all subjects treated with BRAFV600 mutant relapsed or refractory HGG. Further details on the population are provided in protocol Section 5.
2. Primary Variable: BOR by independent review as per RANO criteria.
3. Treatment: dabrafenib plus trametinib, regardless of treatment discontinuation.

Handling of intercurrent events:

- **Discontinuation of study treatment for any reason:** Per treatment policy strategy, tumor assessment data collected after discontinuation of study treatment for any reason will be used to derive BOR.
- **Start of new anti-neoplastic therapy**: Per while on treatment strategy, tumor assessments collected before start of new anti-neoplastic therapy will be used to derive BOR. Tumor assessments collected on/after the start of new therapy will not be considered for evaluation of BOR.

Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria. See section 2.5.2 for details.

Sensitivity analyses for primary endpoint/estimand will be performed using the evaluable set, with all other aspects of the estimand as defined above. Additionally, analyses with response as assessed by the investigator (instead of by central review) will be done under the same estimand attributes.

5.6.2 Handling of missing values not related to intercurrent event

Subjects in FAS with unknown or missing BOR will be noted as such in the appropriate tables/listings and counted as non-responders in the analysis of ORR. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be "Unknown". If no valid post-baseline tumor assessments are available, the BOR must be "unknown" unless progression is reported.

For the purpose of primary analysis, subjects with a BOR of "unknown" (UNK) will be treated as non-responders in estimating the ORR in the FAS.

5.6.3 Supplementary analysis

A supplementary analysis for the primary estimand will be done as defined below:

1. Population: all subjects treated with BRAFV600 mutant relapsed or refractory HGG. Further details on the population are provided in protocol Section 5.
2. Treatment: dabrafenib plus trametinib, regardless of treatment discontinuation or start of new anti-neoplastic therapy.
3. Variable: BOR by independent review as per RANO criteria.

Handling of intercurrent events:

- **Discontinuation of study treatment for any reason** - Per treatment policy strategy, tumor assessment data collected after discontinuation of study treatment for any reason other than PD will be used to derive BOR.
- **Start of new anti-neoplastic therapy**- Per treatment policy strategy, tumor assessment data collected after start of anti-neoplastic therapy will be used to derive BOR.

Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria.

6 Reference

4. American Academy of Pediatrics. (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics, 114, 555-76.
5. Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-22.
6. Brookmeyer R and Crowley J. (1982) A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.

7. Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
8. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
9. Fleming S, Thompson M, Stevens R, et al. (2011) Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 377: 1011-18.
10. Hummel TR., Wagner L, Ahern C., et al. (2013) A pediatric phase 1 trial of vorinostat and temozolomide in relapsed or refractory primary brain or spinal cord tumors: a children's oncology group phase 1 consortium study. Pediatr. Blood Cancer. 60: 1452-7.
11. Kalbfleisch JD and Prentice RL. (2002) The Statistical Analysis of Failure Time Data. Wiley Series in Probability and Statistics.
12. Lashford LS, Thiesse P, Jouvet A, et al. (2002) Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J. Clin Oncol. 24:4684-91.
13. Neuenschwander B, Branson M and Gsponer T. (2008) Critical aspects of the Bayesian approach to Phase I cancer trials. Statistics in Medicine, 27, 2420-2439.
14. Nicholson HS, Kretschmar CS, Krailo M, et al. (2007) Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer. 110:1542–1550.
15. Rijnbeek PR, Witsenburg M, Schrama E, et al. (2001) New normal limits for the paediatric electrocardiogram. Eur Heart J. 22: 702-11.
16. Ruggiero A, Cefalo G, Garre ML, et al. (2006) Phase II trial of temozolomide in children with recurrent high-grade glioma. J Neurooncol. 77:89-94
17. Smith B, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT and Forgue ST. (2000) Confidence Interval Criteria for Assessment of Dose Proportionality. Pharmaceutical Research, 17(10), 1278-83.
18. Warren KE, Gururangan S, Geyer JR, et al. (2012) A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: a Pediatric Brain Tumor Consortium study. J. Neurooncol.106: 643–649.
19. World Health Organization (WHO) Multicentre Growth Reference Study Group. (2009) WHO Child Growth Standards: Growth velocity based on weight, length and head circumference: Methods and development. Geneva: World Health Organization, http://www.who.int/childgrowth/en/.
20. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg. 1997;13:388-391.

NOVARTIS

Clinical Development

DRB436/Dabrafenib, TMT212/Trametinib

CDRB436G2201 / NCT02684058

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)

Statistical Analysis Plan (SAP) for LGG cohort

Final CSR

Author:	Trial Statistician
Document type:	SAP Documentation
Document status:	Final
Release date:	17-May-2023
Number of pages:	69

Document History – Changes compared to previous final version of SAP

Version	Date	Changes
Final 1.0	12-May-2023	

Table of contents

List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BOR	Best Overall response
CBR	Clinical Benefit Rate
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose Administration Record
DOR	Duration Of Response
ECG	Electrocardiogram
eCRF	electronic Case Report Forms
ECHO	Echocardiogram
EoT	End of Treatment
FAS	Full Analysis Set
HGG	High-Grade Glioma
IRT	Interactive Response Technology
LGG	Low-Grade Glioma
LLN	Lower Limit of Normal
MRI	Magnetic Resonance Imaging
NMQ	Novartis MedDRA Query
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	PharmacoKinetics
PR	Partial Response
PRO	Patient-Reported Outcome
PROMIS	Patient-Reported Outcome Measurement Information System
QT	Q to T interval
QTcF	QT interval Corrected using Fridericia method
RANO	Response Assessment in Neuro-Oncology
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDS	Standard Deviation Score

SOC	System Organ Class
SMQ	Standardized MedDRA Query
TBIL	Total Bilirubin
TTR	Time To Response
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the randomized Low-Grade Glioma (LGG) cohort of the final clinical study report (CSR) of study CDRB436G2201, a multi-center, global, open-label, phase II study conducted in children and adolescent patients with BRAF V600 mutation positive LGG or relapsed or refractory High-Grade Glioma (HGG). This SAP will be used for the final analysis for the LGG cohort. All planned analyses for the HGG cohort are described in a separate SAP.

The content of this SAP is based on protocol CDRB436G2201 amendment version 05. All decisions regarding the final analysis, as defined in this SAP document, have been made prior to the final database lock.

1.1 Study design

This study combines two pediatric glioma cohorts (HGG and LGG) into a single multi-center, open-label, phase II study.

The HGG cohort of the study is a single arm cohort that will evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive relapsed or refractory HGG tumors. For more details on the design of HGG cohort, refer to the protocol.

The LGG cohort of the study is a randomized comparison of dabrafenib with trametinib versus standard chemotherapy in the treatment of chemotherapy naïve children and adolescent patients with BRAF V600 mutant LGG whose tumor is unresectable and who require systemic treatment. BRAF V600 mutation-positive tumor was assessed locally, or at a Novartis designated central reference laboratory if local BRAF V600 testing was unavailable. Approximately 102 patients (male or female children or adolescent patients between ≥12 months and <18 years of age with *BRAF* V600 mutation positive LGG with progressive disease (PD) following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression) will be randomized in a 2:1 ratio to either dabrafenib plus trametinib or carboplatin with vincristine. The primary objective of the LGG cohort is to compare the antitumor activity of dabrafenib in combination with trametinib to the combination of carboplatin and vincristine, as measured by overall response rate (ORR) by central independent review assessment using response assessment in neuro-oncology (RANO, 2017) criteria in the Full Analysis Set (FAS). ORR as measured by investigator review, duration of response (DOR), progression-free survival (PFS), time to response (TTR), and clinical benefit rate (CBR) assessed by investigator and independent central review, overall survival (OS), patient-reported outcomes (PRO) from the patient-reported outcome measurement information system (PROMIS) questionnaire, palatability, pharmacokinetics (PK), and the safety and tolerability profile of dabrafenib and trametinib are secondary endpoints.

Patients on dabrafenib and trametinib therapy may continue to receive the assigned study treatment until disease progression by RANO criteria or loss of clinical benefit as determined by the investigator, unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, or study is terminated by the sponsor. Patients on carboplatin with vincristine chemotherapy will receive one course of induction (10 weeks of treatment with 2 weeks of rest), followed by 8 cycles of

maintenance chemotherapy (6 weeks per cycle consisting of 4 weekly treatments plus 2 weeks of rest). Duration of treatment with carboplatin with vincristine will continue for the prescribed number of cycles as tolerated or unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, or study is terminated by the sponsor. Patients randomized to the carboplatin with vincristine treatment arm will be allowed to crossover to receive dabrafenib in combination with trametinib treatment after centrally confirmed and RANO-defined disease progression.

Patients receiving dabrafenib with trametinib who have disease progression by RANO criteria may continue study treatment if the investigator determines that patient has clear evidence of clinical benefit from study treatment, continuing study treatment may be in the best interest for the patient, and the patient/legal guardian is willing to continue on study treatment and sign the Informed Consent for treatment beyond progression. The decision to continue study treatment after PD must be documented in the patient records and electronic case report form (eCRF) after every tumor evaluation. In this case, the patient will continue assessments as defined in the study protocol section 7. An End of Treatment visit will be performed when patients permanently discontinue study treatment.

Patients who discontinue dabrafenib with trametinib treatment or complete carboplatin with vincristine treatment without disease progression by RANO criteria will continue tumor assessments as part of the post treatment follow-up outlined in the study protocol section 7 until central independently confirmed disease progression by RANO criteria or death irrespective of start of new anti-neoplastic therapy.

Patients who discontinue study treatment and efficacy follow-up, and have completed the post-treatment skin examination will enter the post treatment follow-up period during which survival will be collected every 3 months. During the survival follow-up, subsequent anti-neoplastic therapies initiated after study treatment discontinuation will be collected.

All patients will be followed for survival for at least 2 years after the last patient first study treatment (except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation).

The final analysis will be performed when all patients in both cohorts have been followed for survival for at least 2 years from last patient first study treatment, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

1.2 Study objectives and endpoints

A list of all study objectives and endpoints is given below. For the final CSR, not all study objectives will be reported, as they have already been analyzed in the primary analysis. This is documented in the corresponding SAP section for each objective.

Objective	Endpoint
Primary	
To 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 RANO criteria.	ORR, proportion of patients with a best overall confirmed Complete Response (CR) or Partial Response (PR) by central independent review per Response Assessment in Neuro-Oncology (RANO) criteria.
Secondary	
1. Evaluate ORR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by investigator review. 2. Evaluate the DOR of dabrafenib in combination with trametinib versus carboplatin with vincristine by both investigator and central independent review. 3. Evaluate PFS of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review. 4. Evaluate TTR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review. 5. Evaluate CBR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review 6. Evaluate the overall survival of dabrafenib in combination with trametinib versus carboplatin with vincristine. 7. Evaluate 2-year OS estimates of dabrafenib in combination with trametinib versus carboplatin with vincristine. 8. Evaluate the safety and tolerability of dabrafenib in combination with trametinib versus carboplatin with vincristine. 9. Evaluate the palatability of dabrafenib and trametinib 10. Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population 11. Assess patient reported outcomes of dabrafenib in combination with trametinib versus carboplatin with vincristine	1. ORR by investigator review assessment per RANO criteria. 2. DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria. 3. PFS, defined as time from date of randomization to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria 4. TTR, calculated as the time from the date of randomization to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria 5. CBR is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria. 6. OS, defined as the time from date of randomization to death due to any cause. 7. 2-year OS estimates 8. Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO. 9. Palatability questionnaire data 10. Plasma concentration-time profiles of dabrafenib, its metabolites and trametinib and PK parameters 11. Change from baseline in PROMIS Parent Proxy scale - Global Health 7+2
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

A unique cut-off date will be determined for the final analysis, corresponding to the last patient last visit date on the study. The analysis cut-off date will be established at the end of the study when all patients in both cohorts have been followed up for survival for at least 2 years from last patient first treatment, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event [AE]) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations. Note that for the final analysis, the cut-off date will be defined such that no data are collected beyond the cut-off date, i.e., all collected data will be included in the analysis.

All events with start date before or on the cut-off date and not having a documented end date will be reported as ‘ongoing’. This approach applies, in particular, to AE and concomitant medication records.

General analysis conventions

Pooling of centers: unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by frequency counts and percentages; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

Study treatment will refer to dabrafenib and trametinib or carboplatin and vincristine combination. ***Study drug*** will refer to each component of study treatment.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment was administered as per the Dosage Administration eCRF. (Example: if first dose of dabrafenib is administered on 05-Jan-2015, and first dose of trametinib is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015). For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment was administered as per Dose Administration Record (DAR) eCRF. (Example: if the last dabrafenib dose is administered on 15-Apr-2014, and the last dose of trametinib is administered on 17-Apr-2014, then the date of last administration of study treatment is on 17-Apr-2014). Note that for Vincristine and Carboplatin last exposure is different from last administration, please see Section 2.4.1 for further details on the derivation of last exposure.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. AE onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, palatability, Karnofsky/Lansky performance status, etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., tumor assessment, survival time, disease progression, tumor response, and patient-reported outcomes (PRO)) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

The reference day for all calculations for the analysis of crossover subjects will be first date when a non-zero dose of either dabrafenib or trametinib was administered.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as the "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include PRO.

For safety evaluations, the last available assessment on or before the date of start of study treatment is defined as the "baseline" assessment. In the rare case that time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline. If there is more than one record on the same day of screening the highest value would be considered as baseline. For laboratory data, if there is more than one record on the same day of screening, then records from central laboratory should take precedence over local laboratory records.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For safety reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date). For crossover patients who start crossover therapy prior to last dose + 30 days, the on-treatment period will end on the day before the first dose of crossover treatment.
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Notes: if data on clock time is available in the clinical database (e.g. for time of blood/urine sample taken, ECG performed, etc. and first study treatment administration), a more precise

distinction between pre-treatment and on-treatment periods is encouraged to be used. If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize Karnofsky/Lansky performance status, physical exam, vital signs, ECG, and laboratory data collected over time (including unscheduled visits), the assessments will be time slotted. Time windows will be defined for descriptive summary by visit. The following general rule will be applied in creating the assessment windows: if more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If two or more assessments within a time window are equidistant from the target date or on the same date, then the maximum will be used. For growth and ECG analysis, if two assessments within a time window are equidistant from the target date or on the same date, then the mean will be used. For laboratory data, if two assessments within a time window are equidistant from the target date or on the same date, then records from central laboratory should take precedence over local laboratory records. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for Karnofsky/Lansky performance status/Urinalysis

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1[a]	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7
End of treatment (EoT)		
EoT	Within 30 days after last dose	Earliest data available on or after EoT date up to and

Time Window	Planned Visit Timing	Time Window Definition
		including 30 days after EoT
Post treatment [b]		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14

[a]Study Day 1 = start date of study treatment
[b]Post treatment study day 1=end of treatment date + 1 day

Table 2-2 Time windows for physical exam/vital signs/hematology/chemistry

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1[a]	≤ Study Day 1
Week 2 Day 1	Study Day 8	Study Days 6 – 10
Week 3 Day 1	Study Day 15	Study Days 13 – 17
Week 4 Day 1	Study Day 22	Study Days 20 – 24
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7
End of treatment (EoT)		
EoT	Within 30 days after last dose	Earliest data available on or after EoT date up to and including 30 days after EoT
Post treatment[b]		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7 30	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14

[a]Study Day 1 = start date of study treatment
[b]Post treatment study day 1=end of treatment date + 1 day

Table 2-3 Time windows for ECG/Visual Acuity

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1[a]	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 16 Day 1	Study Day 106	Study Days 99 – 113
Week 32 Day 1	Study Day 218	Study Days 211 – 225
Week 48 Day 1	Study Day 330	Study Days 323 – 337
Week 72 Day 1	Study Day 498	Study Days 491 – 505
Every 16 weeks thereafter		
Week y=16+16*k (with k = 1, 2, …)	Study Day (16+16*k-1)*7+1	Study Day (16+16*k-1)*7+1-7 to (16+16*k-1)*7+1+7
End of treatment (EoT)		
EoT	Within 30 days after last dose	Earliest data available on or after EoT date up to and including 30 days after EoT

[a]Study Day 1 = start date of study treatment

For all analyses regarding abnormal assessments or analyses based on worst or best post-baseline value (laboratory, ECGs, vital signs, Karnofsky/Lansky performance status, echocardiogram [ECHO], ophthalmologic exam, dermatologic exam, [redacted] etc.), all post-baseline values will be included (scheduled, unscheduled, repeat).

Time windows will be defined for descriptive summary of PRO data by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered. Data obtained at the end of treatment will be classified as other assessment in the corresponding time window. The end of treatment assessment will be included if collected within 30 days of the last dose intake.

Table 2-4 Time windows for PRO

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1[a]	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7
Every 16 weeks thereafter		

Time Window	Planned Visit Timing	Time Window Definition
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7
End of treatment (EoT)		
EoT	Within 30 days after last dose	Earliest data available on or after EoT date up to and including 30 days after EoT
Post treatment[b]		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7 30	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14
[a]Study Day 1 = randomization date [b]Post treatment study day 1=end of treatment date + 1 day		

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the sources specified in Table 2-5.

Table 2-5 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RANO) assessment date	Evaluation is marked as ‘done’.
Laboratory	Sample collection marked as ‘done’.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will NOT be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a DAR) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from ‘Survival information’ eCRF. If the day is missing from the date of last contact, it will be imputed to the 15th day of the month and year of last contact only if derived from the survival page.

The last contact date will be used for censoring of patients in the analysis of OS.

2.2 Analysis sets

Full Analysis Set

The FAS comprises all patients to whom study treatment has been assigned by randomization regardless of whether or not treatment was administered. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure. This population will be the primary population for efficacy analyses.

Safety Set

The **Safety Set** includes all patients who received at least one dose of any component of the study treatment. Subjects will be analyzed according to the study treatment they actually received where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

Evaluable Set

The **Evaluable Set** (ES) consists of all evaluable patients in the FAS who meet all of the following four criteria:

- centrally confirmed measurable disease, and
- centrally confirmed positive BRAF V600 mutation, and
- an adequate tumor assessment at baseline (An adequate tumor assessment at baseline refers to baseline measurable disease assessed by investigator and confirmed by central independent reviewer per RANO criteria), and
- either 1) a follow-up tumor assessment at week 8 day 1 visit or later (any assessment on or after day 43 allowing for the time-window around the visit) or 2) disease progression at any time or 3) have discontinued for any reason.

The evaluable set will be used for sensitivity analyses as defined in Section 2.5 and Section 2.7.

Crossover Set

The **Crossover Set** (CS) comprises the subset of patients who were randomized to carboplatin with vincristine control arm and elected to crossover to receive dabrafenib in combination with trametinib treatment after centrally confirmed and RANO-defined disease progression. Only subjects who received at least one dose of crossover treatment will be included in the crossover set.

Patient Classification:

Patients may be excluded from the analysis populations defined above based on specific patient classification rules defined in Table 2-6. Reasons leading to exclusion from analysis sets will be listed.

Table 2-6 Patient classification rules for analysis sets

Analysis set	Criteria leading to exclusion
FAS	Not applicable
Safety Set	No dose of study medication
Evaluable Set	Not centrally confirmed measurable disease at baseline, Not centrally confirmed BRAF V600 mutant, Patients who do not have an adequate tumor assessment at baseline Patients who do not have a follow-up tumor assessment at least 43 days after starting treatment unless disease progression is observed before that time or patient discontinued for any reason.

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis data sets. The date on which a patient withdraws full consent is recorded in the eCRF.

Death events may be used in the analysis if captured from public records (registers), local law and subject informed consent permitting.

Additional data for which there is a separate informed consent, collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroups of interest

Efficacy

No subgroup analyses of efficacy data are planned for the final CSR. [redacted]

Safety

Safety subgroup analyses will use the same method as for the analysis in the safety analysis set. Key safety analyses including:

- Overview of AEs:
  - AEs, regardless of relationship to study drug, by primary system organ class (SOC) and preferred term (PT)
  - AEs related to the study drug, by primary SOC and PT

- Serious AEs, regardless of relationship to study drug, by primary SOC and PT

will be repeated on safety set in the following subgroups:

- Age group at enrollment (12 months- <6 years, 6 -< 12 years, 12 -< 18 years)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment group and for all patients, and listings will be reported by treatment group to assess baseline comparability. No inferential statistics will be provided.

For this final analysis, no analyses will be performed on basic demographic and background data, diagnosis and extent of cancer, medical history or other baseline data. As there have been no changes to patient enrollment since the primary analysis, the analyses performed for the primary analysis can be referred to for all baseline data.

2.3.1 Patient disposition

The number (%) of patients in the FAS who completed treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided: % based on the total number of FAS patients:

- Number (%) of patients who were randomized (based on data from IRT system);
- Number (%) of patients who were randomized but not treated (based on 'DAR' eCRF page not completed for any study treatment component);
- Primary reason for not being treated (based on 'End of Treatment Disposition' eCRF page);
- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered);
- Number (%) of patients who completed treatment (based on the 'End of Treatment Disposition' page not completed);
- Number (%) of patients who completed treatment and do not have RANO-defined progression of disease assessed by investigator (based on the 'End of Treatment Disposition' page not completed and no PD reported on the RANO pages);
- Number (%) of patients who are completed treatment post RANO-defined progression of disease assessed by investigator (based on the 'Confirmation of Favorable Clinical Benefit from Study Treatment' page, the 'End of Treatment Disposition' not completed , and PD reported on the RANO pages);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Disposition' page)

- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Disposition' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post Treatment Phase Disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post Treatment Phase Disposition' page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Phase' or 'End of Post Treatment Phase Disposition' page).
- Number (%) of patients who have enrolled in the long-term follow-up study G2401. (based on the 'EOT_Rollover' disposition page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by treatment group. All protocol deviations will be listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment group, separately for each component of study treatment (dabrafenib, trametinib, carboplatin, and vincristine). The duration of exposure will also be presented for the study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by treatment group. The number (%) of patients with a dose re-escalation will also be summarized by treatment group.

Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to any combination partner.

Duration of exposure to study treatment (day*s*) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the latest of the last dates of exposure to any combination partner (see Table 2-7 Definition of last date of exposure of study drug).

Summary of duration of exposure of study treatment in appropriate time units based on clinically meaningful time intervals (eg 8-<24, 24-<56, 56-<112, >= 112 (weeks)) will include categorical summaries and continuous summaries (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum) using appropriate units of time.

Duration of exposure to combination partner

Duration of exposure to dabrafenib (days) = (last date of exposure to dabrafenib) – (date of first administration of dabrafenib) + 1.

Duration of exposure to trametinib (days) = (last date of exposure to trametinib) – (date of first administration of trametinib) + 1.

Duration of exposure to carboplatin overall (days) = (last date of exposure to carboplatin as defined in Table 2-7) – (date of first administration of carboplatin) + 1.

Duration of exposure to vincristine overall (days) = (last date of exposure to vincristine as defined in Table 2-7) – (date of first administration of vincristine) + 1.

Induction phase:

Carboplatin is dosed as weekly IV infusions on weeks 1 to 4, and on weeks 7 to 10 followed by 2 weeks of rest in the ***induction phase***. Vincristine is dosed as weekly IV bolus infusion for 10 weeks followed by 2 weeks of rest in the ***induction phase***. The induction phase refers to the first 12 weeks of dosing (i.e from day of first dose of carboplatin or vincristine until 84 days).

The ***last date of exposur***e to carboplatin or vincristine in the induction phase is calculated including the rest periods (2 weeks). If subjects continued on to maintenance therapy, the last date of exposure in induction phase is the day before the start of maintenance therapy. If the subject does not continue on to maintenance therapy, the last date of exposure is calculated using the planned cycle duration, i.e. the last date of exposure is the date of first administration (of carboplatin or vincristine) in induction + 83 days. If the subject dies or if the data cutoff date is prior to the calculated date of last exposure, the date will be capped at the date of death or data cutoff.

Maintenance phase:

Maintenance phase will continue for up to a total of 8 cycles, each cycle will be 6 weeks in duration and consists of 4 weekly doses of carboplatin followed by 2 weeks of rest, and three weekly doses of vincristine given concomitantly with the first 3 weeks of carboplatin , followed by three weeks of rest. The maintenance phase refers to the dosing after the first 12 weeks, and will be identified by having at least 9 non-zero doses of Carboplatin, or at least 11 non-zero doses of Vincristine. For Carboplatin/Vincristine, maintenance cycle week1 dates are defined by the following non-zero doses: dose 9/dose 11, dose 13/dose 14, dose 17/dose 17, dose 21/dose 20, dose 25/dose 23, dose 29/dose 26, dose 33/dose 29, and dose 37/dose 32, respectively.

The ***last date of exposur***e to carboplatin or vincristine in the induction phase is calculated including the rest periods (2 or 3 weeks). The last date of exposure is calculated using the planned cycle duration, i.e. the last date of exposure is the date of last week 1 administration (of carboplatin or vincristine) in maintenance + 41 days. If the subject dies or if the data cutoff

date is prior to the calculated date of last exposure, the date will be capped at the date of death or data cutoff. The ***number of cycles*** of maintenance therapy will be determined as the following total number of non-zero doses:

- Carboplatin: 1 cycle – 9 to 12 doses; 2 cycles – 13-16 doses; 3 cycles – 17 to 20 doses; 4 cycles – 21 to 24 doses; 5 cycles – 25 to 28 doses; 6 cycles – 29 to 32 doses; 7 cycles – 33 to 36 cycles; 8 cycles – ≥ 37 doses.
- Vincristine: 1 cycle – 11 to 13 doses; 2 cycles – 14-16 doses; 3 cycles – 17 to 19 doses; 4 cycles – 20 to 22 doses; 5 cycles – 23 to 25 doses; 6 cycles – 26 to 28 doses; 7 cycles – 29 to 31 cycles; 8 cycles – ≥ 32 doses.

Duration of exposure to carboplatin and vincristine (days) will be calculated by treatment phase (induction and maintenance phase) and overall (if applicable) as:

Duration of [study drug] exposure (days) in induction phase = (Date of first week1 dose of [study drug] in maintenance – 1 day) - (date of first administration of [study drug]) + 1, for those who entered maintenance. For those who did not enter maintenance therapy, duration of maintenance will be defined as [minimum (date of first administration of [study drug] + 83 days, date of death, date of data cutoff) - (date of first administration of [study drug]) + 1.

Duration of [study drug] exposure (days) in maintenance phase = [minimum(Date of last week1 dose of [study drug] in maintenance + 41 days, date of death, date of data cutoff)] - (date of first week1 dose of [study drug] in maintenance) + 1.

Table 2-7 Definition of last date of exposure of study drug

Scenario	Definition of last date of exposure of study drug	Example
Carboplatin, Vincristine	The planned end date of the last cycle in which the last non-zero dose of the investigational drug was last administered (i.e. last week 1 date of administration + (planned interval duration of either induction or maintenance, as applicable))	
	If carboplatin or vincristine was permanently discontinued during induction, set the last date of exposure equal to the planned end date of induction.	Example 1: Subject discontinues during induction therapy. The last date of exposure is the first date of administration + 83 days.
	If carboplatin or vincristine was permanently discontinued during maintenance, set the last date of exposure equal to the planned end date of the last cycle, last week 1 administration date + 41 days.	Example 2: Subject discontinues during maintenance therapy after receiving the week 45 dose. The week 43 (C dose 29/V dose 26) dose date was 21Jan2021. The last date of exposure is the 21Jan2021 + 41 days = 03Mar2021.
	If carboplatin or vincristine was not permanently discontinued, set the last date of exposure equal to the data cut-off date. Note: If the patient died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the date of last	Example 3: if carboplatin or vincristine was not permanently discontinued prior to or on the data cut-off date, the last date of exposure is the data cut-off date

Scenario	Definition of last date of exposure of study drug	Example
	contact, respectively. If the derived last date of exposure goes beyond the data cut-off date, it should be truncated to the date of data cut-off.	
Dabrafenib, Trametinib	Date of last administration of a non-zero dose of the study drug.	Example 4: A patient had a permanent discontinuation of the study drug on 06Jan2016 after being put on a temporary interruption since 01Jan2016. In this case the last date of exposure is 31Dec2015.

Summary of duration of exposure to each combination partner will include categorical summaries based on clinically meaningful time intervals (8-<24, 24-<56, 56-<112, >= 112 (weeks)) and using descriptive statistics (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum) using appropriate units of time.

Cumulative dose and average daily dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment component, respectively. Average daily dose is defined as [Cumulative dose (dosing unit) / Number of dosing days]; drug free days are not counted as dosing days.

Cumulative dose and average daily dose will be summarized both in mg and mg/kg for dabrafenib and trametinib. Total actual cumulative dose (mg/kg) of dabrafenib and trametinib is calculated as the sum of the daily doses in mg/kg, where the mg/kg dose on any particular day is calculated as the dose in mg divided by the current weight (collected as per the visit schedule). Total actual cumulative dose (mg) of dabrafenib and trametinib is calculated as the sum of the daily doses in mg.

Cumulative dose and average dose per cycle will be summarized in mg/m^2 for carboplatin and vincristine. Total actual cumulative dose of carboplatin or vincristine is calculated as the sum of the cumulative dose.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of study drug administration. For dabrafenib and trametinib, the planned dose (mg) will be taken from the planned dose (mg) times the frequency from the first dosing record. Planned dose for carboplatin and vincristine is defined below. The planned cumulative dose will not be summarized/listed. It will be used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered over the duration for which the patient is on the study treatment as documented in the DAR eCRF page. For patients who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the patient is assumed to have taken a non-zero dose during dosing periods.

Dose intensity and relative dose intensity

Dose of dabrafenib and trametinib will be defined in the units of mg, and taken from the DAR eCRF. Dose of carboplatin and vincristine will be defined in units of mg/m^2, calculated as the administered dose received in mg/m^2 as taken from the DAR eCRF.

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (*unit of dose / unit of time*) = Actual Cumulative dose (*unit of dose*) / Duration of exposure to study treatment (*unit of time*).

For dabrafenib and trametinib, the unit of dose is mg and the unit of time is days; for carboplatin and vincristine, the unit of dose is mg/m^2 and the unit of time is weeks. [Note that for subjects < 12 kg in weight, the unit of dose for vincristine is mg/kg. If such subjects are enrolled in the study, their dosing data will be summarized separately.]

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (*unit of dose / unit of time)* = Planned Cumulative dose (*unit of dose*) / Duration of exposure (*unit of time*).

For carboplatin, the PDI is 116.67 mg/m^2/week, based on 6-week cycles with dosing of 175 mg/m^2 at weeks 1 to 4 only.

For vincristine, the PDI depends on the subject's weight and also on the treatment phase.

For subjects with weight ≥ 12 kg:

- during the induction phase, the PDI is 1.25 mg/m^2/week, based on 1.5 mg/m2 weekly *10 over 12 weeks.
- during the maintenance phase, the PDI is 0.75 mg/m^2/week, based on 1.5 mg/m2 weekly *3 over 6 weeks.

For subjects with weight < 12 kg:

- during the induction phase, PDI is 0.042 mg/kg/week , based on 0.05 mg/kg weekly *10 over 12 weeks.
- during the maintenance phase, the PDI 0.025 mg/kg/week, based on 0.05 mg/kg weekly *3 over 6 weeks.

Relative dose intensity (RDI) is defined as follows:

RDI (%) = [DI (*unit of dose / unit of time*) / PDI (*unit of dose / unit of time*)] x 100.

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components. DI and RDI will be summarized separately for induction and maintenance phase for carboplatin and vincristine.

Summary of RDI will include categorical summaries based on clinically meaningful intervals (≤50%, >50-≤75%, >75-≤90%, >90-≤110%, >110%). Note that for the purposes of DI and RDI derivation only for carboplatin and vincristine, the last date of exposure for the duration of exposure component of this calculation will not consider death date.

Table 2-8 Examples of dabrafenib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg) frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 05Jan2016	125 mg BID	250	No	No	
2	06Jan2016 / 03Feb2016	125 mg BID	200	Yes	No	AE
3	04Feb2016 / 25Feb2016	130 mg BID	260	Yes	No	As per protocol

Duration of exposure (days) = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 125*2*56 days = 14000 mg

Actual cumulative dose = 250*5 + 200*29 + 260*22 = 12770 mg

Dose intensity = 12770 mg / 56 days = 228.04 mg/day

Planned dose intensity = 14000 mg / 56 days = 250 mg/day

Relative dose intensity = DI / PDI = (228.04 mg/day) / (250 mg/day) = 91.2%

Table 2-9 Examples of trametinib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 10Jan2016	0.875 QD	0.875	No	No	
2	11Jan2016 / 15Jan2016	0.875 QD	0	Yes	No	AE
3	16Jan2016 / 25Feb2016	0.75 QD	0.75	Yes	No	AE

Duration of exposure = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 0.875*56 days = 49 mg

Actual cumulative dose = 0.875*10 + 0*5 + 0.75*41 = 39.5 mg

Dose intensity = 39.5 mg / 56 days = 0.705 mg/day

Planned dose intensity = 49 mg / 56 days = 0.875 mg/day

Relative dose intensity = DI / PDI = (0.705 mg/day) / (0.875 mg/day) = 80.6%

Table 2-10 Examples of carboplatin dose administration and exposure

Nominal Visit number	Start/End Date	Phase	Dose Prescribed (mg/m2), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
Week 1 Day 1	01Jan2016 / 01Jan2016	Induction	175 weekly	175	No	No	
Week 2 Day 1	08Jan2016 / 08Jan2016	Induction	175 weekly	0	Yes	No	AE
Week 3 Day 1	15Jan2016 / 15Jan2016	Induction	150 weekly	150	Yes	No	AE
Week 4 Day 1	22Jan2016 / 22Jan2016	Induction	175 weekly	175	No	No	
Week 7 Day 1	13Feb2016 / 13Feb 2016	Induction	175 weekly	175	No	No	
Week 8 Day 1	20Feb2016 / 20Feb2016	Induction	175 weekly	175	No	No	
Week 9 Day 1	28Feb2016 / 28Feb2016	Induction	175 weekly	175	No	No	
Week 10 Day 1	09Mar2016 / 09Mar 2016	Induction	175 weekly	175	No	No	
Week 13 Day 1	31Mar2016 / 31Mar2016	Maintenance C1	175 weekly	175	No	No	
Week 14 Day 1	08Apr2016 / 08Apr 2016	Maintenance C1	175 weekly	175	No	No	
Week 15 Day 1	15Apr2016 / 15Apr2016	Maintenance C1	175 weekly	175	No	No	
Week 16 Day 1	22Apr2016 / 22Apr2016	Maintenance C1	175 weekly	175	No	No	
Week 19 Day 1	14May2016 /14May2016	Maintenance C2	175 weekly	175	No	No	
Week 20 Day 1	21May2016 /21May2016	Maintenance C2	175 weekly	175	No	No	
Week 21 Day 1	28May2016 /28May2016	Maintenance C2	175 weekly	175	No	No	
Week 22 Day 1	04Jun2016 / 04Jun2016	Maintenance C2	175 weekly	175	No	No	

Induction:

Duration of induction = [31Mar2016-1 = 30Mar2016] – 01Jan2016 + 1 = 90 days = 12.86 weeks

Planned dose intensity 116.67 mg/m2/week

Actual cumulative dose induction= 175*6 + 150*1 = 1200 mg/m2

Dose intensity induction = 1200 mg/m2 / 12.86 weeks = 93.3 mg/m2/week

Relative dose intensity induction = DI / PDI = (93.3 mg/m2/week) / (116.67 mg/m2/week) = 80%

Maintenance:

Duration of maintenance = [14May2016 +41=24Jun2016]– 31Mar2016 + 1 = 86 days = 12.29 weeks

Planned dose intensity 116.67 mg/m2/week

Actual cumulative dose maintenance = 175*8 = 1400 mg/m2

Dose intensity maintenance= 1400 mg/m2 / 12.29 weeks = 113.9 mg/m2/week

Relative dose intensity maintenance = DI / PDI = (113.9 mg/m2/week) / (116.67 mg/m2/week) = 97.6%

Table 2-11 Examples of vincristine dose administration and exposure for ≥ 12 kg

Nominal Visit number	Start/End Date	Phase	Dose Prescribed (mg/m2), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
Week 1 Day 1	01Jan2016 / 01Jan2016	Induction	1.5 weekly	1.5	No	No	
Week 2 Day 1	08Jan2016 / 08Jan2016	Induction	1.5 weekly	0	Yes	No	AE
Week 3 Day 1	15Jan2016 / 15Jan2016	Induction	1.0 weekly	1.0	Yes	No	AE
Week 4 Day 1	22Jan2016 / 22Jan2016	Induction	1.5 weekly	1.5	No	No	
Week 5 Day 1	28Jan2016 / 28Jan2016	Induction	1.5 weekly	1.5	No	No	
Week 6 Day 1	04Feb2016 / 04Feb2016	Induction	1.5 weekly	1.5	No	No	
Week 7 Day 1	13Feb2016 / 13Feb 2016	Induction	1.5 weekly	1.5	No	No	
Week 8 Day 1	20Feb2016 / 20Feb2016	Induction	1.5 weekly	1.5	No	No	
Week 9 Day 1	28Feb2016 / 28Feb2016	Induction	1.5 weekly	1.5	No	No	
Week 10 Day 1	09Mar2016 / 09Mar 2016	Induction	1.5 weekly	1.5	No	No	
Week 13 Day 1	31Mar2016 / 31Mar2016	Maintenance C1	1.5 weekly	1.5	No	No	
Week 14 Day 1	08Apr2016 / 08Apr 2016	Maintenance C1	1.5 weekly	1.5	No	No	
Week 15 Day 1	15Apr2016 / 15Apr2016	Maintenance C1	1.5 weekly	0	No	Yes	AE

Induction:

Duration of induction = [31Mar2016-1 = 30Mar2016] – 01Jan2016 + 1 = 90 days = 12.86 weeks

Planned dose intensity induction 1.25 mg/m2/week

Actual cumulative dose induction= 1.5*8 + 1.0*1 = 13 mg/m2

Dose intensity induction = 13 mg/m2 / 12.86 weeks = 1.01 mg/m2/week

Relative dose intensity induction = DI / PDI = (1.01 mg/m2/week) / (1.25 mg/m2/week) = 80.9%

Maintenance:

Duration of maintenance = [31Mar2016 +41=11May2016]– 31Mar2016 + 1 = 42 days = 6 weeks

Planned dose intensity maintenance 0.75 mg/m2/week

Actual cumulative dose maintenance = 1.5*2 + 0 *1 = 3 mg/m2

Dose intensity maintenance = 3 mg/m2 / 6 weeks = 0.5 mg/m2/week

Relative dose intensity maintenance = DI / PDI = 0.5 mg/m2/week) / (0.75 mg/m2/week) = 66.7%

Dose reductions, interruptions, re-escalations or permanent discontinuations

The number of patients who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components. The number of patients who have dose re-escalations will also be summarized.

'Dose interrupted' and 'Dose permanently discontinued' fields from the Dosage Administration Record eCRF pages (DAR) will be used to determine the dose interruptions and permanent discontinuations, respectively. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this block of entries, then it will be counted as one interruption.

Dose Reduction: Only dose change is collected in the eCRF, the number of reductions will therefore be derived programmatically based on the change and the direction of the change. A dose reduction is a dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Note that any dose change due to dispensing or dosing error will not be considered a dose reduction. Note also that any previous dose interruptions and any previous dosing or dispensing errors should be ignored when considering whether a subsequent dose change counts as a dose reduction, i.e., if the new dose is lower than the dose prior to any dose interruption or any dose or dispensing error this would still constitute a dose reduction.

Missing data: If dose is recorded but regimen is missing or entered as 'none', it is assumed that the investigational drug was taken as per-protocol.

Dose Re-escalation: For patients with a dose reduction, a dose re-escalation is where the prescribed dose level is higher than the previous prescribed dose level or where the actual dose administered/total daily dose is higher than the calculated dose amount based on the prescribed dose. An increase will only be considered a dose re-escalation if the reason for dose change is "as per protocol". Note also that any previous dose interruptions and any previous dosing or dispensing errors should be ignored when considering whether a subsequent dose change counts as a dose re-escalation.

2.4.2 Prior, concomitant, on study and post therapies

Prior anti-cancer therapy

The analyses performed for the primary analysis can be referred to for details on prior anti-cancer therapies.

On study Radiotherapy and Surgery

As on study radiotherapy and surgeries are allowed after centrally confirmed radiologic progression of disease or at least a total of 36 months of treatment plus follow-up, whichever comes first. Surgeries and radiotherapies occurring on study will be listed only.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, PT, overall and by treatment group by means of frequency counts and percentages using FAS. In addition, summaries will include best response to the regimen. Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD).

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the WHO Drug Reference Listing (DRL) dictionary that employs the ATC classification system and summarized by lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Non-drug therapies and procedures starting after the start of study treatment will also be summarized by SOC and PT.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Systemic corticosteroid use (flagged using a pre-specified list from the clinical team) will be listed and summarized by lowest ATC class and PT using frequency count and percentages. The total daily dose of systemic corticosteroids can be calculated from the dose per administration and the dose frequency (see Section 5.3). Any corticosteroid use starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. Concomitant medications that have the potential to impact some specific analyses (e.g. efficacy or safety analyses) will be identified prior to database lock. Separate summaries of these concomitant medications will be produced using the appropriate analysis set (e.g. FAS for those potentially affecting efficacy. According to the study protocol, treatment with substances which are strong inhibitors, or inducers of CYP3A4/5

and CYP2C8, or antiretrovirals or herbal medicines or other anti-cancer or anti-investigational drugs should be avoided. However, some patients may take these substances during the treatment period so these concomitant medications will be selected via programming and tabulated and listed in the CSR. Treatment with the prohibited substances mentioned above will be identified in the database as protocol deviations.

2.5 Analysis of the primary objective

The primary objective of the LGG cohort is to compare the antitumor activity of dabrafenib in combination with trametinib versus the carboplatin and vincristine, as measured by ORR to study treatment by central independent review assessment using RANO criteria, in children and adolescent patients with BRAF V600 mutation positive LGG whose tumor is unresectable and who require treatment.

2.5.1 Primary endpoint

ORR is defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) according to RANO criteria (see Appendix 3 of the study protocol). ORR will be calculated based on the FAS using central independent review of tumor assessment data. Only tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. See Appendix 5.5 for primary estimand definition.

Best overall response

The BOR will be assessed based on reported responses across all evaluation time points. Both CR and PR must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met. The next scheduled assessment may be used for purposes of confirmation of response. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease (SD).

BOR for each patient is determined from the sequence of overall responses according to the following rules, up to progression:

- CR = at least two determinations of CR at least 4 weeks apart before progression
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
- SD = requires at least one SD assessment (or better) determined at or beyond the second regularly scheduled tumor assessment (nominally week 16 i.e >= 105 days allowing for the ±1 week visit window) from randomization (and not qualifying for CR or PR).
- PD = progression after start of study treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD at or beyond the second regularly scheduled post-baseline tumor assessment or progression)

If a patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the BOR determination for the primary endpoint. Further anti-neoplastic therapies will be identified via protocol deviations or from the data collected on ‘Anti-neoplastic therapies since last date of study drug’ as appropriate.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed on the FAS. Note that all hypothesis testing was performed at the time of primary analysis and therefore the analysis performed at the time of final analysis will only be considered descriptive and no hypothesis testing will be performed.

ORR will be summarized using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934]. The odds ratio (OR) (dabrafenib + trametinib vs carboplatin + vincristine) and it's 95% confidence interval (CI) will be determined by logistic regression.

2.5.3 Handling of missing values/censoring/discontinuations

Patients with unknown or missing BOR will be counted as non-responders in the analysis of ORR. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the BOR must be "Unknown". For the computation of ORR, these patients will be included in the FAS and will be counted as 'non-responders'. If a subject is determined to have non-measurable disease only, then the category of response can be expanded to include non-CR/non-PD.

A sensitivity analysis will be performed to consider all possible scenarios for patients with unknown response, i.e. progressively from the scenario where all patients with unknown response are considered as non-responders to the scenario where all patients with unknown response are considered as responders. The probability of each scenario based on the observed response rate in the patients without unknown response will also be calculated,

2.5.4 Supportive analyses

As sensitivity analysis, ORR will be calculated and summarized for patients from the Evaluable Set. ORR will be summarized using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413]. Further sensitivity analyses identifying possible outcome scenarios may be performed in the event of patients being randomized but not treated.

New anticancer therapy sensitivity analysis for ORR

The analyses of ORR will be repeated using a stricter ITT approach i.e including all response assessments irrespective of new anti-neoplastic therapy using the FAS. This analysis will only be performed if data permits.

Response evaluations recorded after the initiation of new anti-neoplastic therapy will be included in sensitivity analysis of ORR, (i.e. the occurrence of new anti-neoplastic therapy will be ignored for the analyses). The sensitivity analyses will be performed based on both the investigator and independent review assessments using the FAS. In the summary tables, this approach is referred as 'new anticancer therapy ORR sensitivity.

ORR based on radiographic response by independent review assessment

The analyses of ORR will be repeated based on radiographic response assessed by independent review by only incorporating the radiographic data which includes the lesion measurements

from target lesions, non-target lesions, and new lesion per RANO. Clinical status data and corticosteroid use data will not be considered for the supportive analyses based on radiographic response. Waterfall plot will be presented for this analysis.

Waterfall graphs will be used to depict the anti-tumor activity for independent and investigator assessments. These plots will display the best percentage change from baseline in the sum of the products of perpendicular diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall graphs. Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. A patient with only such assessments will be represented by a special symbol (e.g. ✶) in the waterfall graph. Assessments with "unknown" target lesion response and assessments with unknown overall response will be denoted in the waterfall plots. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of patients with tumor shrinkage and tumor growth. Bars will have different fill patterns for all possible values of overall response. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-12.

Table 2-12 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
case	Target response	Overall lesion response	Include in waterfall?	Non-target response	New lesion?
1	CR/PR/SD	PD	Yes as a bar	PD	any
2	CR/PR/SD	PD	Yes as a bar	any	Yes
3	UNK	UNK or PD	Yes as an x	any	any
4	CR/PR/SD	UNK	Yes as a bar	UNK	No
5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
6	PD	PD	Yes as a bar	any	any

Additionally, swimmer plots of time to onset and DOR based on independent and investigator review will be created for the FAS.

Concordance analysis of ORR

An assessment of the concordance between central independent reviewer assessment and local investigator assessment of the BOR for each patient will be provided. The calculation will be based on the percent agreement (the proportion of response outcomes that agree or match across both independent reviewer and investigator assessments).

Reasons for "Unknown" BOR

Patients with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD and/or unconfirmed CR/PR only occurring prior to week 16 visit

2.6 Analysis of the key secondary objective

Not Applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are to:

- Evaluate ORR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by investigator review per RANO
- Evaluate DOR of dabrafenib in combination with trametinib versus carboplatin with vincristine by both investigator and central independent review per RANO
- Evaluate PFS of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review per RANO
- Evaluate TTR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review per RANO
- Evaluate CBR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review per RANO
- Evaluate OS of dabrafenib in combination with trametinib versus carboplatin with vincristine

2.7.1 Secondary endpoints

ORR by investigator review

The evaluation of ORR will be repeated by investigator review assessment as per RANO criteria based on the FAS and the Evaluable Set separately.

Duration of response

DOR only applies to patients whose BOR is CR or PR according to RANO criteria. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression per RANO or death due to any cause. If a patient has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, DOR will be censored at the date of the last adequate tumor evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier (see Section 2.7.3).

DOR will be analyzed as per investigator and central independent reviewer assessments separately. The analyses of DOR will be based on the FAS and will be repeated based on the Evaluable set.

Progression-free survival

PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be calculated using RANO criteria based on investigators and central independent review of tumor assessments separately. The analysis will include all data observed up-to the cut-off date. If a patient has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier. (See Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment). Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages without supporting evidence satisfying progression criteria per RANO will not be considered disease progression for PFS derivation. The analysis will be based on FAS and Evaluable Set separately.

Time to response

TTR is the time from date of randomization to first documented response of CR or PR (which must be confirmed subsequently) according to RANO criteria. All patients in the FAS will be included in the time to response calculation. Patients who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FPFV - LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other patients.

TTR will be analyzed using investigator and independent reviewer assessments separately.

Clinical Benefit Rate

CBR is defined as the proportion of patients with a BOR of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of 24 weeks. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 23 weeks or later (i.e. $\geq$ 161 days) from randomization, allowing for the $\pm$1 week visit window for tumor assessments.

CBR will be analyzed using investigator and independent reviewer assessments separately. CBR will be calculated using the FAS set and Evaluable Set separately.

Overall Survival

OS is defined as the time from date of randomization to date of death due to any cause.

If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact (Section 2.1.1).

2.7.2 Statistical hypothesis, model, and method of analysis

ORR by investigator review

The analyses performed at the time of final analysis will only be considered descriptive and therefore no inferential analyses or hypothesis tests will be performed for any secondary objective.

ORR assessed by investigator review per RANO criteria will be summarized by treatment group using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413]. The OR and 95% CI will also be presented.

All response data will be listed by investigator and central independent review assessment.

Duration of response

DOR will be listed and summarized by treatment group for all patients in the FAS with confirmed BOR of CR or PR. The distribution of DOR will be estimated using the Kaplan-Meier method and the median DOR will be presented along with 95% CI only if a sufficient number of responses is observed.In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs [Kalbfleisch JD and Prentice RL. (2002)] at several time points (including at least 4, 6,12 and 18 months) will be summarized.

Progression-Free Survival

The distribution of PFS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment group. The median and 25th and 75th percentiles of PFS along with 95% CI will be presented by treatment group. The hazard ratio for PFS will be calculated, along with its 95% CI, using a Cox model. In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at timepoints including 6, 12, 18, and 24 months will be summarized. Censoring reasons will also be summarized.

Time to response

Time to response data will be listed and summarized by treatment group. The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% CI only if a sufficient number of responses is observed. In addition, a responders-only analysis will also be performed using descriptive summary statistics.

Clinical Benefit Rate

CBR will be summarized by treatment group using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413]. The OR and 95% CI will also be presented.

Overall Survival

The survival distribution of OS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment group. The median and 25th and 75th percentiles of OS along with 95% CI will be presented by treatment group. The hazard ratio for OS will be calculated, along with its 95% CI, using a Cox model. In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at timepoints up the maximum follow-up (including at least 6, 12, 18, and 24 months will be summarized).

2.7.3 Handling of missing values/censoring/discontinuations

DOR and PFS

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy, DOR and PFS will be censored at the date of the last adequate tumor before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of randomization will be used.

In particular, DOR and PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is administered; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-13 for censoring and event date options and outcomes for DOR and PFS.

Table 2-13 Outcome and event/censor dates for DOR and PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
New anticancer therapy (including cancer related surgery and radiotherapy) given prior to protocol defined progression (including patients	Date of last adequate assessment on or prior to starting new anti-cancer therapy	Censored

Situation	Date	Outcome
who crossover from the control arm to the treatment arm)		
Death before first PD assessment	Date of death	Event

Censoring pattern of PFS

Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Initiation of new cancer therapy prior to progression
6: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments (see Section 2.7.3 for definition):

1. Analysis cut-off date,
2. Start date of further anti-neoplastic therapy,
3. Date of consent withdrawal,
4. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. ‘Ongoing’,
2. ‘New cancer therapy added’,
3. ‘Withdrew consent’,
4. ‘Lost to follow-up’,

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed. then the PFS censoring reason will always default to ‘Adequate assessment no longer available’. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than the interval of 2 missing tumor assessments then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced for PFS by investigator and central independent reviewers. The censoring patterns will be compared between investigator and central independent reviewers.

Clinical Benefit Rate

Patients with unknown or missing BOR will be counted as non-responders in the analysis of CBR.

OS

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date patient was alive, i.e., last contact date (see Section 2.1.1).

2.7.4 Supportive analyses

DOR, and PFS based on radiographic response by independent review assessment

The analyses of DOR, and PFS will be repeated based on radiographic response assessed by independent review by only incorporating the radiographic data which includes the lesion measurements from target lesions, non-target lesions, and new lesion per RANO. Clinical status data and corticosteroid use data will not be considered for the supportive analyses based on radiographic response.

New anticancer therapy sensitivity analysis for DOR and PFS

The analyses of DOR and PFS will be repeated using an ITT approach i.e including all response assessments irrespective of new anti-neoplastic therapy using the FAS.

Response evaluations and events (i.e. RANO documented disease progression or death) recorded after the initiation of new anti-neoplastic therapy will be included in sensitivity analyses of DOR and PFS, (i.e. the occurrence of new anti-neoplastic therapy will be ignored for the analyses). The sensitivity analyses will be performed based on both the investigator and independent review assessments using the FAS and using the same statistical methods for DOR and PFS described in Section 2.7.2. In the summary tables, this approach is referred as ‘new anticancer therapy DOR sensitivity analysis’ and ‘new anticancer therapy PFS sensitivity analysis’.

2.8 Safety analyses

All safety analyses will be based on the safety set unless otherwise specified.

2.8.1 Adverse events (AEs)

AEs are coded using MedDRA terminology. The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary SOC and for each PT using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A

patient with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PT will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational group (dabrafenib and trametinib).

The following AE summaries will be produced by treatment group: overview of AEs and deaths (number and % of patients with any AE, treatment-related AE, serious adverse events (SAE), fatal AE, AE leading to discontinuation, AE leading to dose reduction/interruption, AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose adjustment and/or interruption, leading to dose reduction, and leading to fatal outcome. In addition, a summary of SAEs with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same PT).

For legal requirements of clinicaltrials.gov and EudraCT, two required tables for on-treatment AEs which are not SAEs with an incidence greater than and equal to 5% and on-treatment SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set.

2.8.1.1 Adverse events of special interest / grouping of AEs

All AE groupings for a clinical program are stored in the electronic Case Retrieval Strategy Sheet (eCRS) with clear versioning and reference to the MedDRA version used.

All adverse event of special interest (AESI) definitions or AE grouping need to be specified in the eCRS. If an eCRS update is necessary, the final version needs to be available in a reasonable time ahead of the DBL. The eCRS version should be included in a footnote of the AESI tables.

Data analysis of AESIs

An AESI is a grouping of AEs that are of scientific and medical concern specific to dabrafenib and trametinib. These groupings are defined using MedDRA terms, standardized MedDRA queries (SMQ), high-level group terms), high-level terms and PT. Customized Novartis MedDRA queries (NMQ) may also be used. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized. Any AESI categories with zero events will also be displayed in the summary tables.

AESI for dabrafenib and trametinib are:

- Skin related toxicities
- Ocular events
- Cardiac related events

- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Hypertension
- Pyrexia
- Pre-Renal and intrinsic renal failure
- Uveitis
- New primary //secondary malignancy
- Hypersensitivity
- Hyperglycemia
- Venous thromboembolism
- Pancreatitis
- Neutropenia

Summaries of these AESIs will be provided by treatment group, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, fatal outcome, etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths including on-treatment and post-treatment deaths will be produced by SOC and PT.

All deaths will be listed for the Safety set, post-treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.8.3 Laboratory data

Data handling

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Data analysis

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of lab parameter values over time (baseline and selected on-treatment timepoints) should be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBIL), alanine aminotrasnferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN

- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

Potential Hy's Law events are defined as those patients with occurrence of AST or ALT > 3xULN and TBL > 2xULN and missing ALP or ALP < 2xULN at any time during the on-treatment period. Note that the criteria relating to combined elevations of AST (or ALT) and TBL are based on the peak values at any post-baseline time for a subject.
For patients with abnormal ALT or AST baseline values, a clinically significant liver safety signal corresponding to Hy's law is defined by : [ALT or AST > 3xbaseline] OR [ALT or AST >8xULN], whichever is lower, combined with [TBIL >2xbaseline AND >2xULN].

A figure displaying time course of hepatic function tests (ALT, AST, TBL, ALP) in patients meeting Hy's criteria will be displayed in the Safety Set. Additonally, evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be produced to display ALT and AST values by TBL values in units of ULN.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG Data handling

In case the study requires electrocardiogram (ECG) replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

ECG Data analysis

Standard 12-lead ECGs including PR, QRS, QT, QTcF, and HR intervals will be obtained local for each patient during the study. ECG data will be read and interpreted locally.

The number and percentage of patients with notable ECG values will be presented by treatment group:

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

The normal range for HR is displayed in Table 2-14. The number and percentage of patients with notable values will be presented.

Table 2-14 Recommendation for normal heart rate per age group and gender

Age group	1-<3 years	3-<5 years	5-<8 years	8-<12 years	12-<16 years	16-<20 years	20-<30 years
HR (bpm) Boys	(95, 155)	(75, 125)	(60, 115)	(55, 100)	(50, 100)	(50, 105)	(45, 95)
HR (bpm) Girls	(95, 180)	(80, 125)	(70, 115)	(60, 110)	(50, 100)	(45, 105)	(50, 100)

Age should be age at assessment. Data shown as upper limit of normal, lower limit of normal for HR= heart rate. Ref.: adapted from Rijnbeek et al. 2001 and Rijnbeek et al. 2014

The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. A listing of all ECG assessments will be produced and notable values will be flagged. A separate listing of only the patients with notable ECG values may also be produced. In the listings, the assessments collected during the post-treatment period will be flagged.

The denominator to calculate percentages for each category is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline ECG notable value is defined as a post-baseline value that meets the criterion post-baseline but did not meet the criterion at baseline.

For each ECG parameter, descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized. Descriptive statistics at worst post-baseline and changes from baseline to worst post-baseline will also be summarized separately.

For each of the QTc and QT intervals, shift tables based on notable parameter categories (<450, 450-<481, 481-<501, ≥501 ms) at baseline and the worst post-baseline value observed.

Frequency counts and percentages of patients with newly occurring post-baseline qualitative ECG abnormalities (morphology) will be summarized. The denominator to calculate percentages is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline qualitative ECG abnormality is defined as a post-baseline abnormal finding which was not present at baseline.

Patients with notable ECG interval values and newly occurring qualitative ECG abnormalities will be listed and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

ECHO Data handling

ECHO data will be analyzed based on local reported results. The summaries will include all ECHO assessments performed no later than 30 days after the last date of study drug. All ECHO assessments will be listed, and those collected later than 30 days after study drug discontinuation will be flagged in the listing.

The same modality (ECHO or MUGA) for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) should be used to follow a patient throughout the study. The absolute change from baseline values will not be calculated for any patients where the post-baseline value was determined by a cardiac scan modality that is different than the one used to determine baseline value.

ECHO Data analysis

Absolute change from baseline in LVEF will be summarized in the worst case post-baseline. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- No change or any increase
- Any decrease:
  - > 0 - <10% Decrease
  - 10 - <20% Decrease
  - ≥20% Decrease
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

ECHO assessments of LVEF will be listed for each patient including absolute change from baseline at each assessed time interval. The values of potential clinical importance will also be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters are being collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-145 below.

Table 2-15 Criteria for notably abnormal vital signs

Vital sign (unit)	Clinically notable criteria High		Low	
Systolic blood pressure [mmHg]	≥ 95th percentile of the age and height group[1]		≤ 5th percentile of the age and height group[1]	
Diastolic blood pressure [mmHg]	≥ 95th percentile of the age and height group[1]		≤ 5th percentile of the age and height group[1]	
Body temperature [°C]	≥ 38.4°C		≤ 35.0°C	
Pulse rate [bpm][2]	12-18 months	> 140	12-18 months	< 103
	18-24 months	> 135	18-24 months	< 98
	2-3 years	> 128	2-3 years	< 92
	3-4 years	> 123	3-4 years	< 86
	4-6 years	> 117	4-6 years	< 81
	6-8 years	> 111	6-8 years	< 74
	8-12 years	> 103	8-12 years	< 67
	12-15 years	> 96	12-15 years	< 62
	≥ 15 years	> 92	≥ 15 years	< 58
Weight	increase from baseline of ≥ 2 BMI-for-age percentile categories[3]		decrease from baseline of ≥ 2 BMI-for-age percentile categories[3]	

bpm=beats per minute; CDC= Centers for Disease Controls and prevention; NHLBI= National Heart, Lung, and Blood Institute;

[1] Blood pressure percentiles are calculated for each blood BP record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; 377: 1011-18.

[3] BMI-for-age percentiles categories are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/) and are shown in Section 5.4.1;

Note: For patients less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the recumbent length; for patients over 228 months- old, percentiles are not available and will be considered as missing.

The number and percentage of patients with notable vital sign values (high/low) will be presented by treatment group.

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP. Baseline is defined as the last non-missing value prior to or coinciding with first dose. The worst post-baseline value refers to the worst post-baseline value on treatment.

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure. For each parameter, only patients with a value at both baseline and post baseline (on treatment) will be included. For pulse parameter, the

subject can be counted in both low and high categories and with a subject contributing to multiple age categories as data is collected over time.

A listing of all vital sign assessments will be produced by visit and notable values will be flagged. A separate listing of only the patients with notable vital sign values may also be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Performance status

The Karnofsky and Lansky performance status scale (Table 2-16) will be used to assess physical health of patients:

Table 2-16 Performance status criteria

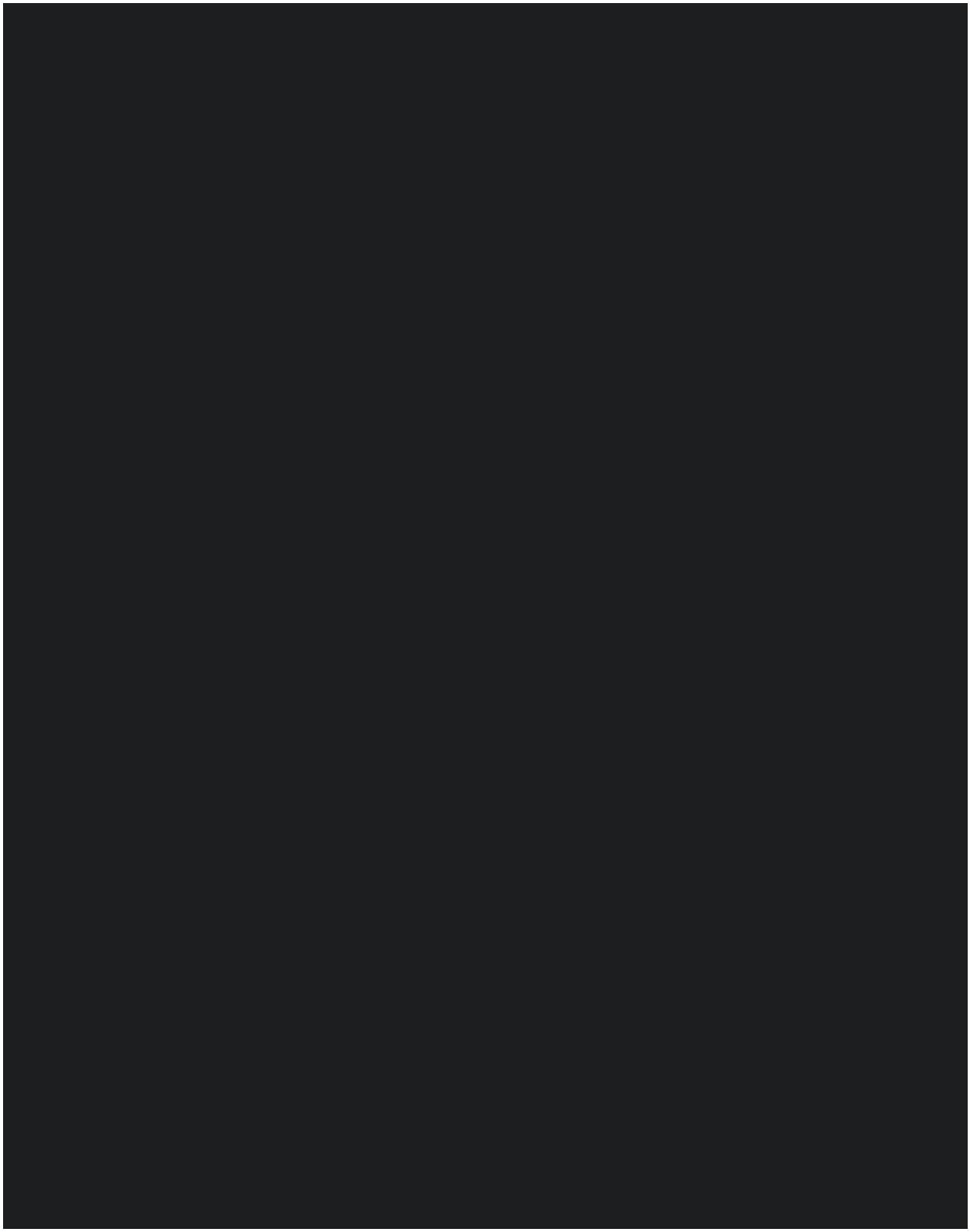
PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be in multiples of 10			
Karnofsky (age ≥16 years of age)		**Lansky** (age <16 years)	
Score	**Description**	**Score**	**Description**
100	Normal, no complaints no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity, minor signs of symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort, some signs of symptoms of disease.	80	Active, but tires quickly.
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play, keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.

Frequency counts and percentages of patients in the score category of 100, 90, 80, 70, and < 70 will be provided by time point based on the windows defined in Section 2.1.1. A summary of change from baseline by scheduled visits will be performed by treatment group, as well as the worst case post-baseline (lowest value during the on-treatment period) and the best case post-baseline (highest value during on-treatment period) changes during the study.

A supporting listing will also be provided.

2.8.4.4 Dermatological Evaluation

Skin examination results will be summarized by frequency counts and percentages of patients in each category (normal, abnormal) by scheduled time points by each treatment group. A supporting listing will also be provided.



2.8.4.7 Growth and development (Height and Weight)

Growth data consist of height, BMI, height SDS, BMI SDS, height velocity SDS, weight velocity SDS, height velocity and weight velocity.

Height and weight will be summarized at 6-month intervals during the on-treatment period, using the SDS, velocity and velocity SDS. The relevant height and weight values for each 6-month period are defined using time windows, as defined in Table 5-4. The z-scores will allow identification of potential outliers.

The formula used to calculate the SDS and height and weight velocities are provided in the Appendix 5.4.2.

Note that BMI SDS are reported instead of weight SDS as no reference data for weight are provided by the WHO for age beyond 10.

Height and BMI SDS and height and weight velocity SDS will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, minimum, maximum) for each time window (at Baseline and thereafter allowing informal comparison of growth data), as well as by presenting number of patients with SDS values lower/higher than 5^{th}/95^{th} percentiles respectively.

Box plots will be plotted for each time window. A shift table to compare baseline SDS to the worst on-treatment SDS categorized as Low (SDS <- 1.645), High (SDS > 1.645) or Normal (-1.645 ≤ SDS ≤ 1.645) will be produced for height and BMI SDS. Another shift table to compare the baseline height SDS to the last available on-treatment height SDS categorized according to the main percentile lines (>95^{th}, 95^{th} to 90^{th}, 90^{th} to 75^{th}, 75^{th} to 50^{th}, 50^{th} to 25^{th}, 25^{th} to 10^{th}, 10^{th} to 5^{th} and ≤5^{th} percentile) will be produced.

In addition, a mixed model will be used to estimate differences of change from baseline in height SDS between treatment groups. A mixed model with height SDS as the response variable and time, gender, and treatment as explanatory variables will be fit using PROC MIXED. See Appendix 5.4.5 for model specifications and further details.

2.8.4.8 Ophthalmologic exam

Visual acuity will be converted from snellen to logMAR scale as defined in Holladay 1997 (21), and categorized as the following change from baseline:

- Improvement: ≥ 0.2 logMAR improvement (decrease in logMAR)
- Stable: neither ≥ 0.2 logMAR improvement nor worsening, where
- Worsening: ≥ 0.2 logMAR worsening (increase in logMAR)

Visual acuity categories at each time point, as well as best and worst category on treatment will be presented. For patients who enrolled on the study due to impaired vision (blindness, deterioration of visual acuity, nystagmus, or vision abnormal), change in visual acuity using the logMAR scale will be plotted with reference lines to show start and end of study treatment. [redacted] Data from ophthalmologic exams will be listed by treatment group.

[redacted]

2.8.4.10 Palatability

Analysis of palatability was performed at the time of primary analysis, at which time all data had already been collected. No further palatability analysis will be performed for the Final CSR.

2.8.4.11 Additional analyses

Time to first occurrence

Time to first occurrence of an event is defined as time from start of study treatment to the date of first occurrence of this event (or first event within an AE grouping), i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.

For Kaplan-Meier analyses of time to occurrence, in the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- end date of on-treatment period
- data cut-off date
- withdrawal of informed consent date.

Failure curves (ascending Kaplan-Meier curves) will be constructed. Median together with 95% CI as well as 25th percentile and 75th percentile will be presented.

In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

2.9 Pharmacokinetic endpoints

PK analyses were performed at the time of primary analysis, at which time all data had already been collected. No further PK analysis will be performed for the Final CSR

2.10 Patient-reported outcomes

PRO will only be evaluated for the LGG cohort. The FAS will be used for analyzing PRO data unless specified differently. One PRO questionnaire: the PROMIS Parent Proxy Global Health 7+2 will be used to evaluate the quality of life of patients between treatment groups. The 7+2 item parent proxy pediatric global health measure include a one global health score plus a single score from pain and a score from fatigue interference item which are scored independently. These two items are administered but do not contribute to the global health score. Rather, they are “signal” items that provide initial score estimates for pain interference and fatigue.

The PRO instruments are planned to be administered on Day 1, at Week 5 and every 8 weeks until Week 56, then every 16 weeks thereafter until disease progression per RANO criteria.

The baseline is defined as the last PRO assessment on or prior to the treatment start date.

Compliance to the schedule of administration of PRO assessments will be summarized by treatment group, for baseline and post-baseline on treatment assessments and scheduled post-treatment time points. The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

1. yes
2. yes, fully completed
3. yes, partly completed
4. no, patient missed scheduled assessment visit
5. no, patient refused due to poor health
6. no, patient refused (unrelated to health)
7. no, study staff felt patient was too ill
8. no, questionnaire not available in appropriate language
9. no, institutional error
10. no, device not available
11. no, technical issues
12. no, other
13. no

A summary of the number and percentage of patients with questionnaire completion of 'yes' or 'no' (where categories 1-3 are counted as 'yes' and categories 4-13 are counted as 'no') will also be summarized by treatment group and time point.

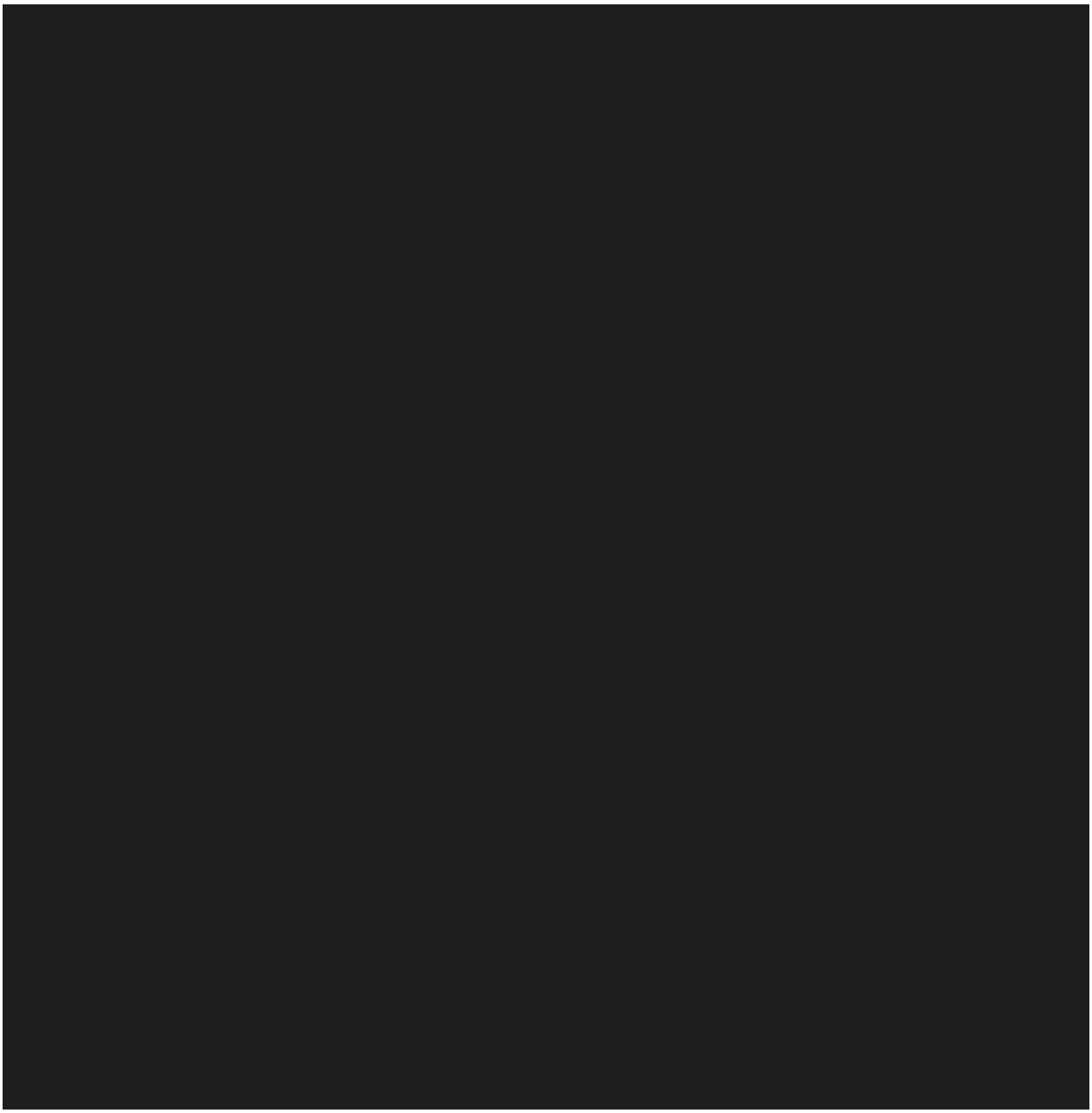
Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide PROMIS global scoring manual, Christopher B. Forrest, 2013. No imputation procedures will be applied for missing items or missing assessments.

Descriptive statistics will be used to summarize the scored scales of PROMIS Parent Proxy Global Health 7+2 at each scheduled assessment time point for each treatment group. Additionally, change from baseline in the scale at the time of each assessment will be summarized. Subjects with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

In addition, a repeated measures model for longitudinal data will be used to estimate differences in PROMIS Parent Proxy Global Health 7+2 scores between treatment groups. The modeling will be done on the actual score. Note that the modeling of the change in score or the actual score is equivalent since adjustment for baseline score is considered CHMP Guideline on adjustment for baseline covariates 2015. The repeated measures model will include terms for fixed effects of treatment, visit, baseline value as main effects, and an interaction term for treatment by visit. The differences in least square means between the treatment groups and corresponding 95% CI will be presented by visit. This analysis will be restricted to patients with an evaluable baseline score and at least one evaluable post-baseline score. All data collected

until end of treatment (including the end of treatment assessment) will be included in the analysis. Note that only data collected under treatment (i.e. while the patient is treated) will be included. The end of treatment assessment will be included if collected within 30 days of the last dose intake.

As a first approach, an unstructured correlation matrix will be used to model the correlation within patients. The structure of the correlation matrix will be investigated and simplified using likelihood ratio tested if appropriate.



2.13 Crossover Phase

Baseline

Baseline is defined as the most recent non-missing value before the first dose of study treatment (dabrafenib plus trametinib) on the crossover treatment period. Baseline values will be established prior to the start of the crossover phase.

Response will be determined separately for the randomized phase and the crossover phase. Baseline lesion assessments will be re-established prior to initiation of crossover therapy and response will be calculated based on the appropriate baseline for each respective phase.

On-treatment assessment/event and observation periods

For AE reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: up to 90 days prior to the first dose on the crossover phase
2. ***on-treatment period***: from date of first administration of crossover study treatment to 30 days after date of last actual administration of study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of crossover study treatment.

The reference date for both efficacy and safety measures in the Crossover phase is the date of first dose of dabrafenib or trametinib on the crossover treatment period.

The tables and listings for the randomized and crossover phases will be separate. Note: Analyses specified as for the Randomized phase will only include data prior to crossover except for analyses of OS. Similarly analyses specified for the crossover phase will only use data from after the date of crossover.

Only key summary tables will be provided for the crossover phase for example; disposition, treatment discontinuation, exposure, deaths, AE/SAEs, ORR, and time to response. Listings will be provided for the crossover data.

3 Sample size calculation

The sample size calculation was based on the primary analysis and is not applicable for the final analysis.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of date of last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year (yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EoT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of that specific record, if the imputed date is < start date of that record:

Use the start date of that record

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications, and for assigning pre/on/post treatment periods.

5.1.2.1 Other imputations

Incomplete date of antineoplastic medications, radiotherapy, surgery, initial diagnosis of cancer or date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

AEs are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the CTCAE version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Systemic corticosteroids

Systemic corticosteroids should be flagged based on a list provided by the clinical team. Further details will be provided in the programming datasets specifications (PDS).

The total daily dose can be calculated by multiplying the dose per administration by the factor specified in Table 5-3 according to the specified dosing frequency.

Table 5-3 Multiplicative factors to calculate total daily dose

Frequency	Meaning	Multiply dose per administration
BID	Twice per day	2
BIW	Twice per week	0.2857
Continuous	-	*Set to missing*
Daily	Once per day	1
Once	-	1
Other	-	*Set to missing*
PRN	As required	*Set to missing*
QD	Once per day	1
QH	Once per hour	24
Q2H	Once every 2 hours	12
Q3H	Once every 3 hours	8
Q4H	Once every 4 hours	6
Q5H	Once every 5 hours	4.8
Q6H	Once every 6 hours	4
Q8H	Once every 8 hours	3
Q12H	Once every 12 hours	2
Q14H	Once every 14 hours	1.7143
Q18H	Once every 18 hours	1.3333
Q24H	Once every 24 hours	1
QID	Four times per day	4
QM	Once per month	0.0328
Q2M	Once every 2 months	0.0164
Q3M	Once every 3 months	0.0110
QOD	Once every other day	0.5
QW	Once per week	0.1429
Q2W	Once every 2 weeks	0.0714
Q3W	Once every 3 weeks	0.0476
Q4W	Once every 4 weeks	0.0357
TID	Three times per day	3
TIW	Three times per week	0.4286
Unknown	-	*Set to missing*
Weekly	Once per week	0.1429
5x per day	Five times per day	5
6x per day	Six times per day	6
7x per day	Seven times per day	7
8x per day	Eight times per day	8

5.4 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of white blood cells (WBC).

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.4.1 Growth data

SDS will be calculated using the current formulae provided by the WHO as follows:

1. Calculate $z_{ind} = \frac{\left(\frac{X}{M}\right)^{L} - 1}{LS}$
2. If $|z_{ind}| \leq 3$, SDS = z_{ind}
   If $z_{ind} > 3$, SDS = 3 + (X – SD3*pos*) / SD23*pos*
   If $z_{ind} < -3$, SDS = -3 + (X – SD3*neg*) / SD23*neg*

where:

- *X* is height in centimeters or BMI in kilograms/m^2,
- *L*, *M* and *S* are height or BMI-, sex- and age-specific reference values from the WHO Growth Charts.
- SD3*pos* is the cutoff 3SD calculated by the LMS method:
  SD3*pos* = M * $(1 + LS*3)^{1/L}$

- SD3*neg* is the cutoff -3SD calculated by the LMS method:
  $SD3neg = M * (1 + LS*(-3))^{1/L}$
- SD23*pos* is the difference between the cutoffs 3SD and 2SD:
  $SD23pos = M * (1 + LS*3)^{1/L} - M * (1 + LS*2)^{1/L}$
- SD23*neg* is the difference between the cutoffs -2SD and -3SD:
  $SD23neg = M * (1 + LS*(-2))^{1/L} - M * (1 + LS*(-3))^{1/L}$

Height-for-age and BMI-for-age L, M and S reference values for males and females are available under [http://www.who.int/childgrowth/standards/en/] (for patients aged between 0 to 5 years old) and [http://www.who.int/growthref/en/] (for patients aged between 5 to 19 years old). These correspond to the latest available international references available at this time and described in the 2007 Bulletin of the WHO [Mercedes de Onis et al 2007]. Note: use age in months at time of assessment "(visit date – date of birth) / 30.4375" rounded down to the nearest whole month for corresponding values of L, M and S. SDS is actually a Z score that measures the distance from the population mean in units of standard deviations. That is, SDS < 0 refers to values lower than the population mean, and for example SDS ≤ -1.645 refers to values in the lowest 5%.

The SDS score can be converted to a percentile assuming a standard normal distribution [mean=0, standard deviation =1]. Percentiles will also be grouped into the following categories: <1st percentile, ≥1 to <3, ≥3 to <5, ≥5 to <15, ≥15 to <25, ≥25 to <50, ≥50 to <75, ≥75 to <85, ≥85 to <95, ≥95 to <97, ≥97 to <99, ≥99.

Note that BMI is reported instead of weight as no reference data are provided by the WHO for age beyond 10.

Height velocity is defined as follows:

Height velocity (cm/6-months) = (height in time window *k* – height in time window *k-1*) ÷ ([assessment date in time window *k* – assessment date in time window *k-1*] ÷ [365.25/2]), and similarly for weight velocity.

Velocity SDS is calculated as (velocity – mean) / standard deviation, where mean and standard deviation are obtained as the height-, weight-, sex- and age-specific values [Baumgartner et al 1986], where the age category immediately above the patient's exact age (at the assessment date in time window *k*) should be used. Velocity SDS will only be calculated for time window *k* if data also exists for time window *k-1*, since calculating across multiple units of 6 months requires more than one reference value to be taken into account.

Table 5-3 summarizes the time windows for growth data, where windows are centered at every 6 months after start of study treatment. Although height and weight are collected more frequently than every 6 months (post-enrollment), this choice of time window length was made to reflect the degree of accuracy in the reference values (every 6 months) that will be used in the calculation of summary variables of growth.

In case of multiple assessments falling into the time window interval, the closest to the target date will be considered. For example, if there are three assessments falling under the time window of Day 85 to 252, then the closest one to target day of 168 will be considered. If two assessments are equidistant from target date, the average will be considered of those respective assessments.

Table 5-4 Time windows for growth data (height SDS, height velocity, weight velocity, BMI SDS)

Planned assessment	Time window
Baseline	Days ≤1
Month 6 (Day 168)	Days 85 – 252
Month 12 (Day 336)	Days 253 – 420
Month 18 (Day 504)	Days 421 – 588
Month xx (Day xx * 28)	Days ((xx – 3) * 28 + 1) – Day ((xx + 3) * 28)
End of Treatment (EoT)	Earliest data available on or after EoT date up to and including 30 days after EoT

Day 1 = date of first intake of study drug
xx = Every 6 months

5.4.2 Bone Age

Bone age SDS will be calculated as (bone age – chronological age) / standard deviation) where the chronological age is the age in months at the time of the X-ray evaluation and standard deviation is the sex- and age-specific standard deviation, as defined in the table below:

Table 5-5 Variability in Bone Age

Chronologic Age in Months	Boys Standard Deviation	Girls Standard Deviation
12	2.1	2.7
18	2.7	3.4
24	4	4
30	5.4	4.8
36	6	5.6
42	6.6	5.5
48	7	7.2
54	7.8	8
60	8.4	8.6
66	9.1	8.9
72	9.3	9
84	10.1	8.3
96	10.8	8.8
108	11	9.3
120	11.4	10.8
132	10.5	12.3
144	10.4	14
156	11.1	14.6
168	12	12.6
180	14	11.2
192	15	15
204	15.4	15.4

If the chronologic age falls between two values in the table above, the closest age should be used. If the chronologic age falls exactly in the middle between 2 values in the table above, then the age above the chronologic age should be used.

Table 5-6 Time windows for bone data

Planned assessment	Time window
Baseline	Days ≤ 1
Month 6 (Day 168)	Days 85 – 252
Month 12 (Day 336)	Days 253 – 420
Month 18 (Day 504)	Days 421 – 588
Month xx (Day xx * 28)	Days ((xx – 3) * 28 + 1) – Day ((xx + 3) * 28)
End of Treatment (EoT)	Earliest data available on or after EoT date up to and including 30 days after EoT

Day 1 = date of first intake of study drug
xx = Every 12 months

5.5 Statistical models

5.5.1 Primary analysis

Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial CI (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI and exact one-sided p-value for the hypothesis test of the *null proportion* (0.10).

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used by changing **level** = "No". From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$LCL_{LEVEL="Yes"}\ (\%) = 100\% - UCL_{LEVEL="No"}\ (\%)$$

$$UCL_{LEVEL="Yes"}\ (\%) = 100\% - LCL_{LEVEL="No"}\ (\%)$$

Multiplicity adjustment

Not applicable.

5.5.2 Key secondary analysis

Not applicable.

5.5.3 Secondary efficacy analysis

Kaplan-Meier estimates

To analyze time to event endpoints (TTR, DOR, PFS and OS). An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. The TIME statement will include a variable with survival times and a (right) censoring variable with a value of 1, representing censoring. Kaplan-Meier survival and failure function estimates from this procedure will be used to construct the Kaplan-Meier figures.

Median survival will be obtained along with 95% CI calculated from PROC LIFETEST output using the method of [Brookmeyer R and Crowley J. (1982)]. Kaplan-Meier estimates of the survival function with 95% CI at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collet D (1994).].

Hazard ratio

Hazard ratios will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

An unadjusted Cox model will be used, i.e. the MODEL statement will include the treatment group variable as the only covariate.

Hazard ratio with two-sided 95% CI will be based on Wald test.

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

5.5.4 Implementation of RANO guidelines (protocol Appendix 3)

As described in the protocol, the ORR will be evaluated by RANO criteria for solid tumors. This section provides some details on how to derive these endpoints by RANO and further details are included in the protocol Appendix 3.

The RANO criteria for assessment of LGG differs from that for HGG primarily in that LGG assessments utilize T2/FLAIR imaging rather than contrast enhancement as these tumors rarely enhance while HGG assessments utilize Gadolinium enhanced imaging. LGG cohorts will be assessed per LGG modification of RANO criteria with the exception that minor response will not be evaluated as per protocol.

The major differences between RECIST 1.1 and RANO include:

- The measurability criteria for target lesion by RANO is based on two dimensions i.e two perpendicular diameters are measured for each target lesion;
- Corticosteroids use and clinical status are also considered for determining overall response;
- T2/FLAIR will be used for both measurable and non-measurable disease

Overall Lesion Response Collected on RANO eCRF page

In this study, Independent reviewer reported overall response and Investigator reported overall lesion response will be used for primary and secondary endpoints.

For investigator, the overall response by RANO will be derived based on the collected overall lesion response on eCRF page "RANO Overall Lesion Response" (ZR domain, ZRCAT = "RESPONSE ASSESSMENT IN NEURO-ONCOLOGY", and ZRSCAT = "OVERALL LESION RESPONSE").

For independent reviewer, the overall response by RANO will be derived based on the collected overall lesion response on eCRF page "RANO Overall Lesion Response" (ZR domain, ZRCAT = "RESPONSE ASSESSMENT IN NEURO-ONCOLOGY", and ZRSCAT = "OVERALL RESPONSE").

There will be two evaluations at a given assessment for independent reviewer i.e. primary RANO radiologic review without clinical data (read 1 – ZREVAL = "PRIMARY REVIEW") and a secondary RANO review with clinical data (read 2 – ZREVAL = "SECONDARY REVIEW"). Secondary RANO review (read 2) with clinical data will be used for the primary endpoint of BOR per independent review. Primary review (read 1) will be used in supportive analyses based on radiographic review only, without clinical data.

Calculation of Overall Lesion Response by RANO

Overall lesion responses by RANO are also calculated from the following components:

1. Target lesion measurements;
2. Non-target lesion response;
3. New lesion present (Yes/No);
4. Corticosteroids use;
5. Clinical status.

All these components are collected on the following eCRF pages:

1. RANO target lesion - Measurable enhancing lesion (T1) (ZI domain, ZICAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = "MEASURABLE T2/FLAIR");
2. RANO non-target lesion - Non-measurable enhancing lesion (T1) (ZI domain, ZICAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = " NON-MEASURABLE T2/FLAIR");
3. RANO New Lesion (ZI domain, ZICAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = "NEW");
4. Corticosteroids use and clinical status are collected on the Modified RANO Assessment (ZR domain, ZRCAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = "RESPONSE ASSESSMENT").

All the above components are collected on the same eCRF pages for independent reviewer with the exception of ZICAT = " RESPONSE ASSESSMENT IN NEURO-ONCOLOGY".

Each target lesion by RANO criteria has two perpendicular diameters collected. In order to calculate the target lesion response, the product of the two perpendicular diameters is calculated for each target lesion. Then the sum of the products of diameters of all target lesions is compared to the baseline or nadir to determine the target lesion response.

The non-target lesion response is collected on the field of "Non-target lesion present" in the Modified RANO Assessment page, and is evaluated based on both non-target lesion eCRF pages as shown above. However, no derivation will be performed from individual non-target lesion status to non-target lesion response.

The RANO response/progression criteria are summarized in .

Table 5-7 Summary of the RANO response criteria

	CR	PR	SD	PD
T2/FLAIR	None	≥50% decrease from baseline	<50% decrease from baseline but <25% increase from nadir	≥25% increase from nadir*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA**
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Worsened*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease
*: Progression occurs when this criterion is met
**: Not Applicable (NA): Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration
Note: The minor response category will not be utilized in this study.

Two fields in the Modified RANO Assessment page will not be used for any data analysis in the study: "New enhancement outside radiation field?", "Tumor present in histopathology".

5.5.5 Mixed Model for Height SDS

A mixed model will be used to estimate differences of change from baseline in height SDS between treatment groups. A mixed model with height SDS as the response variable and time, gender, and treatment as explanatory variables will be fit using PROC MIXED.

Two copies of visit number in integer (AVISITN) will be used to proxy the time of measurements. One copy of the time measure AVISITN is created and named TIME to specify the model with a continuous time measure (used for fixed effects) and the other named MONTH to specify the model with a categorical time measure (used for random effects).

In this model, as a first approach, a mixed model with an unstructured variance-covariance matrix will be used to model the correlation within patients. The structure of the correlation matrix and the use of random intercept will be further investigated if the first approach fails to converge. Therefore, we proposed the following sequence of model fits:

1. Step 1: Repeated measures with an unstructured variance-covariance matrix.
2. If it fails to converge, try the random intercept model with a AR(1) variance-covariance matrix for the repeated measures.

Below are the SAS codes for reference.

FIT 1

```
PROC MIXED DATA=SCC METHOD=REML;
        CLASS TRT01AN USUBJID MONTH SEXN;
        MODEL AVAL=TRT01AN TIME TRT01AN*TIME SEXN / SOLUTION DDFM=KENWARDROGER;
        REPEATED MONTH / SUBJECT=USUBJID TYPE=UN;
        ESTIMATE 'slope TRT D+T' TIME 1 TIME*TRT01AN 1 0;
        ESTIMATE 'slope TRT C+V' TIME 1 TIME*TRT01AN 0 1;
        ESTIMATE 'slope (D+T) - (C+V)' TIME*TRT01AN 1 -1;
         LSMEANS TRT01AN / PDIFF CL;
        RUN;
```

FIT 2

```
PROC MIXED DATA=SCC METHOD=REML;
        CLASS TRT01AN USUBJID MONTH SEXN;
        MODEL AVAL=TRT01AN TIME TRT01AN*TIME SEXN / SOLUTION DDFM=KENWARDROGER;
        RANDOM INTERCEPT / SUBJECT=USUBJID;
        REPEATED MONTH / SUBJECT=USUBJID TYPE=AR(1);
        ESTIMATE 'slope TRT D+T' TIME 1 TIME*TRT01AN 1 0;
        ESTIMATE 'slope TRT C+V' TIME 1 TIME*TRT01AN 0 1;
        ESTIMATE 'slope (D+T) - (C+V)' TIME*TRT01AN 1 -1;
         LSMEANS TRT01AN / PDIFF CL;
        RUN;
```

5.6 Estimands

5.6.1 Primary estimand for the primary objective

The primary clinical question of interest is: what is the relative effect of the two treatment strategies in increasing the ORR by independent review as per RANO criteria in children and adolescent subjects with BRAFV600 mutant LGG with PD, regardless of study treatment discontinuation and before start of any new anti-neoplastic therapy.

The justification for the primary estimand is that it will capture the treatment effect of the study drug even after treatment is discontinued, but avoid potential confounding effects of any other new anti-neoplastic therapy.

The primary estimand is characterized by the following attributes:

1. Population: all subjects randomized with BRAFV600 mutant LGG with PD following surgical excision, or non-surgical candidates with necessity to begin first systemic treatment because of a risk of neurological impairment with progression. Further details on the population are provided in protocol Section 5.
2. Primary Variable: BOR by independent review as per RANO criteria.
3. Treatment: the randomized treatment (the investigational treatment dabrafenib plus trametinib or the control treatment vincristine plus carboplatin), regardless of treatment discontinuation.

Handling of intercurrent events:

- **Discontinuation of study treatment for any reason:** Per treatment policy strategy, tumor assessment data collected after discontinuation of study treatment for any reason will be used to derive BOR. This includes subjects who were randomized but not treated.
- **Start of new anti-neoplastic therapy**: Per while on treatment strategy, tumor assessments collected before start of new anti-neoplastic therapy will be used to derive BOR. Tumor assessments collected on/after the start of new therapy will not be considered for evaluation of BOR.

Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria between the treatment arms as assessed by the Mantel-Haenszel chi-squared test. See sections 2.5.2 for details.

Sensitivity analyses for primary endpoint/estimand will be performed using the evaluable set, with all other aspects of the estimand as defined above. Additionally, analyses with response as assessed by the investigator (instead of by central review) will be done under the same estimand attributes.

5.6.2 Handling of missing values not related to intercurrent event

Subjects in FAS with unknown or missing BOR will be noted as such in the appropriate tables/listings and counted as non-responders in the analysis of ORR. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be “Unknown”. If no valid post-baseline tumor assessments are available, the BOR must be “unknown” unless progression is reported.

For the purpose of primary analysis, subjects with a BOR of “unknown” (UNK) will be treated as non-responders in estimating the ORR in the FAS.

5.6.3 Supplementary analysis

A supplementary analysis for the primary estimand will be done as defined below:

1. Population: all subjects randomized with BRAFV600 mutant LGG with PD following surgical excision, or non-surgical candidates with necessity to begin first systemic

treatment because of a risk of neurological impairment with progression. Further details on the population are provided in protocol Section 5.

2. Treatment: the randomized treatment (the investigational treatment dabrafenib plus trametinib or the control treatment vincristine plus carboplatin), regardless of treatment discontinuation or start of new anti-neoplastic therapy.
3. Variable: BOR by independent review as per RANO criteria.
   - Handling of intercurrent events: **Discontinuation of study treatment for any reason** - Per treatment policy strategy, tumor assessment data collected after discontinuation of study treatment for any reason will be used to derive BOR. This includes subjects who were randomized but not treated.

Start of new anti-neoplastic therapy- Per treatment policy strategy, tumor assessment data collected after start of anti-neoplastic therapy will be used to derive BOR. Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria between the treatment arms.

6 Reference

1. American Academy of Pediatrics. (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics, 114, 555-76.
2. Brookmeyer R and Crowley J. (1982) A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
3. CHMP guideline on adjustments for baseline covariates in clinical trials (2015) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184923.pdf
4. Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
5. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
6. Christopher B. Forrest, et al. (2013), Development of the PROMIS_ pediatric global health (PGH-7) measure
7. Fleming S, Thompson M, Stevens R, et al. (2011) Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 377: 1011-18.
8. Hummel TR., Wagner L, Ahern C., et al. (2013) A pediatric phase 1 trial of vorinostat and temozolomide in relapsed or refractory primary brain or spinal cord tumors: a children's oncology group phase 1 consortium study. Pediatr. Blood Cancer. 60: 1452-7.
9. Kalbfleisch JD and Prentice RL. (2002) The Statistical Analysis of Failure Time Data. Wiley Series in Probability and Statistics.
10. Lashford LS, Thiesse P, Jouvet A, et al. (2002) Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J. Clin Oncol. 24:4684-91

11. Lassaletta A, Zapotocky M, Mistry M, et al. (2017). Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. J. Clin Oncol. 35(25): 2934-2941.
12. Neuenschwander B, Branson M and Gsponer T. (2008) Critical aspects of the Bayesian approach to Phase I cancer trials. Statistics in Medicine, 27, 2420-2439.
13. Nicholson HS, Kretschmar CS, Krailo M, et al. (2007) Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer. 110:1542–1550.
14. PROMIS global scoring manual, www.HealthMeasures.net.
15. Rijnbeek PR, Witsenburg M, Schrama E, et al. (2001) New normal limits for the paediatric electrocardiogram. Eur Heart J. 22: 702-11.
16. Rijnbeek PR, van Herpen G, Bots ML, et al (2014) Normal values of the electrocardiogram for ages 16-90 years. Journal of Electrocardiology 47(6): 914-921
17. Ruggiero A, Cefalo G, Garre ML, et al. (2006) Phase II trial of temozolomide in children with recurrent high-grade glioma. J Neurooncol. 77:89-94
18. Smith B, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT and Forgue ST. (2000) Confidence Interval Criteria for Assessment of Dose Proportionality. Pharmaceutical Research, 17(10), 1278-83.
19. Warren KE, Gururangan S, Geyer JR, et al. (2012) A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: a Pediatric Brain Tumor Consortium study. J. Neurooncol.106: 643–649.
20. World Health Organization (WHO) Multicentre Growth Reference Study Group. (2009) WHO Child Growth Standards: Growth velocity based on weight, length and head circumference: Methods and development. Geneva: World Health Organization, http://www.who.int/childgrowth/en/.
21. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg. 1997;13:388-391.

NOVARTIS

Clinical Development

DRB436/Dabrafenib, TMT212/Trametinib

CDRB436G2201 / NCT02684058

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)

Statistical Analysis Plan (SAP) for LGG cohort - Amendment 1

Author:	Trial Statistician
Document type:	SAP Documentation
Document status:	Final
Release date:	30-Sep-2021
Number of pages:	78

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14-Mar-2018	Prior to DB lock	Creation of final version	N/A - First version	NA
20-Sep-2021	Prior to primary DBL	Changes needed for primary analysis	Updated to align with protocol and clarify as needed for study design, and objectives and endpoints.	Section 1.1, 1.2
			Clarifications added to safety set to define actual treatment. Evaluable set patient classification adjusted to correctly identify evaluable patients.	Section 2.2
			[redacted]	[redacted]
			Definitions for induction and maintenance phases added for the chemotherapy arm. RDI definitions were updated to align with other studies.	Section 2.4.1
			Prior anti-cancer therapy summaries updated to align with inclusion/exclusion criteria.	Section 2.4.2
			Clarification added that BOR is determined up to progression.	Section 2.5.1
			Supportive analysis for randomized not treated subjects added, Odds ratio for ORR added, [redacted]	Section 2.5.2, Section 2.5.4. Section 2.7.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Clarification that hierarchical testing will occur at the time of primary analysis.	Section 2.7.1
			Display time points for DOR, PFS and OS updated.	Section 2.7.2
			AESI updated to current standard. Definition of censoring for time to first occurrence of AESI added.	Section 2.8.1.1, Section 2.8.4.11
			Hy's law section updated for new guidance.	Section 2.8.3
			Clarification added for notable abnormal height for patients less than 2 years old. Bone age SDS, growth and development analyses added.	Section 2.8.4.2, Section 2.8.4.6, Section 2.8.4.7
			Visual acuity analysis added.	Section 2.8.4.8
			PK parameters Cavg and Tlast added.	Section 2.9
			PD analysis was not applicable and was removed.	Section 2.10
			PRO longitudinal analysis updated to include visit as a categorical variable instead of continuous.	Section 2.10
			[redacted]	[redacted]
			[redacted]	[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Details added for implementation of RANO guidelines.	Appendix 5.4.4
			Model details for height SDS added.	Appendix 5.4.5
			Estimand language added.	Appendix 5.5

Table of contents

List of abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
b.i.d.	*bis in diem*/twice a day
C_{avg}	Average Concentration
CBR	Clinical Benefit Rate
[redacted]	[redacted]
Cmax	The observed maximum (peak) plasma concentration after drug administration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Event
DILI	Drug-induced liver injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms for EDC
ECHO	Echocardiogram
EDC	Electronic Data Capture
EMA	The European Medicines Agency
eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
FDA	Food and Drug Administration
HGG	High Grade Glioma
HPMC	Hydroxypropylmethyl cellulose
i.v.	intravenous(ly)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board

IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
Kg	Kilogram
LFT	Liver Function Test
LGG	Low Grade Glioma
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NSCLC	Non-small cell lung cancer
o.d.	*omnia die*/once a day
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic analysis set
PD	Progression of disease
p.o.	*per os*/by mouth/orally
PFS	Progression Free Survival
PK	Pharmacokinetics
POS	Probability of Success
PRO	Patient Reported Outcome
PROMIS	Patient Reported Outcome Measurement Information System
QT	Q to T interval (ECG)
QTcF	QT interval corrected using Fridericia method
RANO	Response Assessment in Neuro-Oncology Criteria
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
SAE	Serious Adverse Event
R Value	ALT/ALP in x ULN
SAP	Statistical Analysis Plan
SC	Steering Committee
SDS	Standard Deviation Score
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TBIL	Total bilirubin
TTR	Time to Response
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Low Grade Glioma (LGG) cohort of the clinical study report (CSR) of study CDRB436G2201, a multi-center, global, open-label, phase II study conducted in children and adolescent patients with BRAF V600 mutation positive LGG or relapsed or refractory High Grade Glioma (HGG). This SAP will be used for the primary analysis and final analysis for LGG cohort. All planned analyses for the HGG cohort are described in a separate analysis plan.

The content of this SAP is based on protocol CDRB436G2201 amendment version 05. All decisions regarding primary and final analyses, as defined in the SAP document, have been made prior to database lock.

1.1 Study design

This study combines two pediatric glioma cohorts (HGG and LGG) into a single multi-center, open-label, phase II study.

The HGG cohort of the study is a single arm cohort that will evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive relapsed or refractory HGG tumors. For more details on the design of HGG cohort, refer to the protocol for the HGG cohort SAP.

The LGG cohort of the study is a randomized comparison of dabrafenib with trametinib versus standard chemotherapy in the treatment of chemotherapy naïve children and adolescent patients with BRAF V600 mutant LGG whose tumor is unresectable and who require treatment. BRAF V600 mutation-positive tumor was assessed locally, or at a Novartis designated central reference laboratory if local BRAF V600 testing was unavailable. Approximately 102 patients (male or female children or adolescent patients between ≥12 months and <18 years of age with *BRAF* V600 mutation positive LGG with 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) will be randomized in a 2:1 ratio to either dabrafenib plus trametinib or carboplatin with vincristine. The primary objective of the LGG cohort is to compare the antitumor activity of dabrafenib in combination with trametinib to the combination of carboplatin and vincristine, as measured by ORR by central independent review assessment using RANO criteria in the Full Analysis Set (FAS) population. ORR as measured by investigator review, DOR, PFS, TTR, and CBR assessed by investigator and independent central review, OS, patient reported outcomes from the PROMIS questionnaire, palatability, PK, and the safety and tolerability profile of dabrafenib and trametinib are secondary endpoints.

Patients on dabrafenib and trametinib therapy may continue to receive the assigned study treatment until disease progression by RANO criteria or loss of clinical benefit as determined by the investigator, unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, or study is terminated by the sponsor. Patients on carboplatin with vincristine chemotherapy will receive one course of induction (10 weeks of treatment with 2 weeks of rest), followed by 8 cycles of maintenance chemotherapy (6 weeks per cycle consisting of

4 weekly treatments plus 2 weeks of rest). Duration of treatment with carboplatin with vincristine will continue for the prescribed number of cycles as tolerated or unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, or study is terminated by the sponsor. Patients randomized to the carboplatin with vincristine treatment arm will be allowed to crossover to receive dabrafenib in combination with trametinib treatment after centrally confirmed and RANO-defined disease progression.

Patients receiving dabrafenib with trametinib who have disease progression by RANO criteria may continue study treatment if the investigator determines that patient has clear evidence of clinical benefit from study treatment, continuing study treatment may be in the best interest for the patient, and the patient/legal guardian is willing to continue on study treatment and sign the Informed Consent for treatment beyond progression. The decision to continue study treatment after PD must be documented in the patient records and eCRF after every tumor evaluation. In this case, the patient will continue assessments as defined in the study protocol section 7. An End of Treatment visit will be performed when patients permanently discontinue study treatment.

Patients who discontinue dabrafenib with trametinib treatment or complete carboplatin with vincristine treatment without disease progression by RANO criteria will continue tumor assessments as part of the post treatment follow-up outlined in the study protocol section 7 until central independently confirmed disease progression by RANO criteria or death irrespective of start of new anti-neoplastic therapy.

Patients who discontinue study treatment and efficacy follow-up, and have completed the post-treatment skin examination will enter the post treatment follow-up period during which survival will be collected every 3 months. During the survival follow-up, subsequent anti-neoplastic therapies initiated after study treatment discontinuation will be collected.

All patients will be followed for survival for at least 2 years after the last patient first study treatment (except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation).

The primary analysis will be conducted based on the FAS when all patients have either completed at least 32 weeks of treatment (i.e. at least 24 weeks follow-up after the first post baseline tumor assessment) or have discontinued earlier. No formal interim analysis is planned for the LGG cohort.

Final analysis will be performed when all patients have been followed for survival until 2 years from last patient first study treatment, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

An independent Data Monitoring Committee (DMC) will monitor safety data approximately every 6 months from the start of study enrollment during the conduct of the study.

1.2 Study objectives and endpoints

Objective	Endpoint
Primary	
To 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 RANO criteria.	ORR, proportion of patients with a best overall confirmed Complete Response (CR) or Partial Response (PR) by central independent review per Response Assessment in Neuro-Oncology (RANO) criteria.
Secondary	
1. Evaluate ORR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by investigator review. 2. Evaluate the DOR of dabrafenib in combination with trametinib versus carboplatin with vincristine by both investigator and central independent review. 3. Evaluate PFS of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review. 4. Evaluate TTR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review. 5. Evaluate CBR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review 6. Evaluate the overall survival of dabrafenib in combination with trametinib versus carboplatin with vincristine. 7. Evaluate 2-year OS estimates of dabrafenib in combination with trametinib versus carboplatin with vincristine. 8. Evaluate the safety and tolerability of dabrafenib in combination with trametinib versus carboplatin with vincristine. 9. Evaluate the palatability of dabrafenib and trametinib 10. Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population 11. Assess patient reported outcomes of dabrafenib in combination with trametinib versus carboplatin with vincristine	1. ORR by investigator review assessment per RANO criteria. 2. DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria. 3. PFS, defined as time from date of randomization to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria 4. TTR, calculated as the time from the date of randomization to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria 5. CBR is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria. 6. OS, defined as the time from date of randomization to death due to any cause. 7. 2-year OS estimates 8. Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO. 9. Palatability questionnaire data 10. Plasma concentration-time profiles of dabrafenib, its metabolites and trametinib and PK parameters 11. Change from baseline in PROMIS Parent Proxy scale - Global Health 7+2

Objective	Endpoint
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The primary and final analyses will be performed by Novartis. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

The data for the HGG and LGG cohorts will be analyzed independently with timing of analyses based on specific independent criteria for each cohort outlined in the study protocol. If the requirements for analysis for both HGG and LGG will be met close together, the timing may be adjusted slightly in order to facilitate submission.

Note that there may be a need to support the initial submission of an indication based on the primary analysis data with safety and PK interim data from both cohorts. Thus the initial planning of the primary analysis for a specific cohort should anticipate that a safety interim or update analysis of the other cohort may also be required.

Data included in the analysis

A unique cut-off date for LGG cohort will be determined for all analyses specified in the study protocol. The analysis cut-off date for the primary analysis of study data will be established after all enrolled LGG patients have completed 32 weeks of treatment or have discontinued study. For final analysis, the analysis cut-off date will be established at the end of the study when all patients have been followed up for survival at least 2 years from last patient first treatment, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

For each of the analyses, all statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-

off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication records.

General analysis conventions

Pooling of centers: unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by frequency counts and percentages; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

Study treatment will refer to dabrafenib and trametinib or carboplatin and vincristine combination. ***Study drug*** will refer to each component of study treatment.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the Dosage Administration (e)CRF. (Example: if 1^{st} dose of dabrafenib is administered on 05-Jan-2015, and 1^{st} dose of trametinib is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015). For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per Dose Administration (e)CRF. (Example: if the last dabrafenib dose is administered on 15-Apr-2014, and the last dose of trametinib is administered on 17-Apr-2014, then the date of last administration of study treatment is on 17-Apr-2014). For Vincristine and Carboplatin, please see Section 2.4.1 for further details.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, palatability, Karnofsky/Lansky performance status, PK etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., tumor assessment, survival time, disease progression, tumor response, and patient reported outcomes (PRO)) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include PRO.

For safety evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment. In the rare case that time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For safety reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date). For crossover patients who start crossover therapy prior to last dose + 30 days, the on-treatment period will end on the day before the first dose of crossover treatment.
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Notes: if data on clock time is available in the clinical database (e.g. for time of blood/urine sample taken, ECG performed, etc. and first study treatment administration), a more precise distinction between pre-treatment and on-treatment periods is encouraged to be used. If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize Karnofsky/Lansky performance status, PK, physical exam, vital signs, ECG, laboratory [redacted] data collected over time (including unscheduled visits), the assessments will be time slotted. Time windows will be defined for descriptive summary by visit. The following general rule will be applied in creating the assessment windows: if more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the worst case will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for Karnofsky/Lansky performance status/Urinalysis

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1*	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7 Note: EOT data visit are

Time Window	Planned Visit Timing	Time Window Definition
		included if obtained within 30^ days of last non-0 dose intake.
End of treatment		
End of treatment	N.A.	Data collected under EOT visit, if no data were collected at the EOT visit last available data obtained before EOT
Post treatment [a]		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14
Study Day 1 = start date of study treatment Post treatment study day 1=end of treatment date + 1 day ^30 days is considered to be the time until total drug elimination		

Table 2-2 Time windows for physical exam/vital signs/hematology/chemistry

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1*	≤ Study Day 1
Week 2 Day 1	Study Day 8	Study Days 6 – 10
Week 3 Day 1	Study Day 15	Study Days 13 – 17
Week 4 Day 1	Study Day 22	Study Days 20 – 24
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
End of treatment		
End of treatment	N.A.	Data collected under EOT visit, if no data were collected at the

Time Window	Planned Visit Timing	Time Window Definition
		EOT visit last available data obtained before EOT
Post treatment		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7 30	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14
Study Day 1 = start date of study treatment Post treatment study day 1=end of treatment date + 1 day ^30 days is considered to be the time until total drug elimination		

Table 2-3 Time windows for ECG/Visual Acuity

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1*	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 16 Day 1	Study Day 106	Study Days 99 – 113
Week 32 Day 1	Study Day 218	Study Days 211 – 225
Week 48 Day 1	Study Day 330	Study Days 323 – 337
Week 72 Day 1	Study Day 498	Study Days 491 – 505
Every 16 weeks thereafter		
Week y=16+16*k (with k = 1, 2, …)	Study Day (16+16*k-1)*7+1	Study Day (16+16*k-1)*7+1-7 to (16+16*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
End of treatment		
End of treatment	N.A.	Data collected under EOT visit, if no data were collected at the EOT visit last available data obtained before EOT
Study Day 1 = start date of study treatment Post treatment study day 1=end of treatment date + 1 day ^30 days is considered to be the time until total drug elimination		

Time windows for PK are provided in Section 7.2.3.1 of the study protocol.

For all analyses regarding abnormal assessments or analyses based on worst or best post-baseline value (laboratory, ECGs, vital signs, Karnofsky/Lansky performance status, ECHO, ophthalmologic exam, dermatologic exam, [redacted] etc.), all post-baseline values will be included (scheduled, unscheduled, repeat).

Time windows will be defined for descriptive summary of PRO data by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered. Data obtained at the end of treatment will be classified as other assessment in the corresponding time window. The end of treatment assessment will be included if collected within 30 days of the last dose intake.

Table 2-4 Time windows for PRO

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1*	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
End of treatment		
End of treatment	N.A.	Data collected under EOT visit, if no data were collected at the EOT visit last available data obtained before EOT
Post treatment*		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7 30	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14

Study Day 1 = randomization date

Post treatment study day 1=end of treatment date + 1 day

^30 days is considered to be the time until total drug elimination

*The max duration of carboplatin and vincristine as per COG regimen is approximately 60 months so PRO assessments will be collected for both arms until disease progression

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-5 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RANO) assessment date	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will NOT be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF. If the day is missing from the date of last contact, it will be imputed to the 15th day of the month and year of last contact only if derived from the survival page.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The **Full Analysis Set** (FAS) comprises all patients to whom study treatment has been assigned by randomization regardless of whether or not treatment was administered. According to the intent to treat principle, patients will be analyzed according to the

treatment they have been assigned to during the randomization procedure. This population will be the primary population for efficacy analyses.

Safety Set

The **Safety Set** includes all patients who received at least one dose of any component of the study treatment. Subjects will be analyzed according to the study treatment they actually received where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

Evaluable Set

The **Evaluable Set** (ES) consists of all evaluable patients in the FAS who have centrally confirmed measurable disease, centrally confirmed positive BRAF V600 mutation, an adequate tumor assessment at baseline, and a follow-up tumor assessment at least 8 weeks after starting treatment (unless disease progression is observed before that time) or have discontinued for any reason. An adequate tumor assessment at baseline refers to baseline measurable disease assessed by investigator and confirmed by central independent reviewer per RANO criteria.

The evaluable set will be used for sensitivity analyses as defined in sections 2.5 and 2.7.

Crossover Set

The **Crossover Set** (CS) comprises the subset of patients who were randomized to carboplatin with vincristine control arm and elected to crossover to receive dabrafenib in combination with trametinib treatment after centrally confirmed and RANO-defined disease progression. Only subjects who received at least one dose of crossover treatment will be included in the crossover set.

Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) consists of all patients who receive at least one (full or partial) dose of dabrafenib or trametinib in the randomized phase and provide at least one evaluable pharmacokinetic (PK) blood sample.

A sample is considered evaluable if all of the following conditions are satisfied:

- Patient did not vomit within 4 hours after the dosing of dabrafenib/trametinib prior to sampling;
- For pre-dose samples: have the sample collected before the next dose administration.

Validity of PK samples will be confirmed by checking sampling time window and occurrence of vomiting with respect to time of dose when PK profile is sampled. Only confirmed PK concentrations will be used in the analyses.

Additionally, a sample can be considered to be not evaluable as per scientific judgment of the clinical pharmacology expert. When a sample is considered not evaluable by the clinical pharmacology expert, the reason will be documented.

The PAS will be used in the analysis of PK data. Any blood samples missing blood collection date or time, or missing associated study drug dosing date or time will be excluded.

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific patient classification rules defined in Table 2-6.

Table 2-6 Patient classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety Set	No written inform consent	No dose of study medication
Evaluable Set		Not centrally confirmed measurable disease at baseline, Not centrally confirmed BRAF V600 mutant, Patients who do not have an adequate tumor assessment at baseline, and a follow-up tumor assessment at least 8 weeks (±1 week visit window) after starting treatment unless disease progression is observed before that time.
PK Analysis Set	Relevant PD criterion	Patients who do not have at least one evaluable PK sample as defined above

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis data sets. The date on which a patient withdraws full consent is recorded in the eCRF.

Death events may be used in the analysis if captured from public records (registers), local law and subject informed consent permitting.

Additional data for which there is a separate informed consent, e.g. PK, [redacted] etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroups of interest

Efficacy

The primary efficacy endpoint ORR and secondary endpoint DOR by investigator and central independent review assessments may be summarized by risk categories such as that determined by methylation analysis based on FAS and Evaluable set. The risk categories from methylation data will be specified in a later SAP amendment prior to final database lock [redacted]. Other risk categories that may be considered are radiographic progression as indication to treatment (Y/N), and gross total resection (Y/N).

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and confidence intervals will be provided. The objective of the efficacy subgroup analysis is to assess homogeneity of treatment effect in the above subgroups. In addition, efficacy data for patients enrolled in Japan will also be reported separately.

Safety

Safety subgroup analyses will use the same method as for the analysis in the safety analysis set. Key safety analyses including:

- Overview of AEs
  - AEs, regardless of relationship to study drug, by primary system organ class and preferred term
  - AEs related to the study drug, by primary system organ class and preferred term
  - Serious AEs, regardless of relationship to study drug, by primary system organ class and preferred term

will be repeated on safety set in the following subgroups:

- Age group (12 months- <6 years, 6 -< 12 years, 12 -< 18 years)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients.

Exposure data will be presented by the following subgroups:

- Dabrafenib: Age group (< 12 years, ≥ 12 years)

- Trametinib: Age group (< 6 years, ≥ 6 years)

For data that require a summary table by subgroup, a listing may be sufficient if less than 10% of patients or less than 10 patients are present in each subgroup.

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment group and for all patients, and listings will be reported by treatment group to assess baseline comparability. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment group. Categorical data (e.g. gender, age groups: 12 months-<6 years, 6 -< 12 years, and 12 -< 18 years, race, ethnicity, height, weight, BMI, BSA, Karnofsky/Lansky performance status, [redacted]) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body surface area (BSA)) will be summarized by descriptive statistics (n, mean, median, standard deviation, 25^{th} and 75^{th} percentiles, minimum and maximum). BSA will be calculated using Gehan and George formula: BSA[m2] = 234.94 * (height[cm] ** 0.422) * (weight[kg] ** 0.515) /10000 unless otherwise specified.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, pathology at initial diagnosis, histological grade for initial diagnosis, time since initial diagnosis, presence/absence of target and non-target lesions, BRAF mutation status (local or central result used to determine eligibility, as applicable), and indication to study treatment. Note: Presence/absence of target and non-target lesions will be based on the data collected on RANO target/non-target lesion assessment eCRF pages.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF pages will be summarized and listed by treatment group. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline, including source of patient referral, child bearing potential, [redacted] informed consent will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by treatment group using the FAS. The number (%) of randomized patients included in the FAS will be presented overall and by treatment group. The number (%) of screened and not-randomized patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided: % based on the total number of FAS patients:

- Number (%) of patients who were randomized (based on data from IRT system);
- Number (%) of patients who were randomized but not treated (based on 'DAR' eCRF page not completed for any study treatment component);
- Primary reason for not being treated (based on 'End of Treatment Disposition' eCRF page);
- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered);
- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Disposition' page not completed);
- Number (%) of patients who are still on-treatment and do not have RANO-defined progression of disease assessed by investigator (based on the 'End of Treatment Disposition' page not completed and no PD reported on the RANO pages);
- Number (%) of patients who are still on-treatment post RANO-defined progression of disease assessed by investigator (based on the 'Confirmation of Favorable Clinical Benefit from Study Treatment' page, the 'End of Treatment Disposition' not completed , and PD reported on the RANO pages);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Disposition' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post Treatment Phase Disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post Treatment Phase Disposition' page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Phase' or 'End of Post Treatment Phase Disposition' page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by treatment group. Protocol deviations leading to exclusion from analysis sets will be listed. [redacted]

Analysis sets

The number and percentages (based on the total number of FAS patients) of patients in each analysis set (defined in Section 2.2) will be summarized.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment group, separately for each component of study treatment (dabrafenib, trametinib, carboplatin, and vincristine). The duration of exposure will also be presented for the study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

The Safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to any combination partner.

Duration of exposure to study treatment (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the latest of the last dates of exposure to any combination partner (see Table 2-7 Definition of last date of exposure of study drug).

Summary of duration of exposure of study treatment in appropriate time units based on clinically meaningful time intervals (eg 8-<24, 24-<56, 56-<112, >= 112 (weeks)) will include categorical summaries and continuous summaries (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum) using appropriate units of time.

Duration of exposure to combination partner

Duration of exposure to dabrafenib (days) = (last date of exposure to dabrafenib) – (date of first administration of dabrafenib) + 1.

Duration of exposure to trametinib (days) = (last date of exposure to trametinib) – (date of first administration of trametinib) + 1.

Duration of exposure to carboplatin overall (days) = (last date of exposure to carboplatin as defined in table 2.7) – (date of first administration of carboplatin) + 1.

Duration of exposure to vincristine overall (days) = (last date of exposure to vincristine as defined in table 2.7) – (date of first administration of vincristine) + 1.

Induction phase:

Carboplatin is dosed as weekly IV infusions on weeks 1 to 4, and on weeks 7 to 10 followed by 2 weeks of rest in the ***induction phase***. Vincristine is dosed as weekly IV bolus infusion for 10 weeks followed by 2 weeks of rest in the ***induction phase***. The induction phase refers to the first 12 weeks of dosing (i.e from day of first dose of carboplatin or vincristine until 84 days).

The ***last date of exposur***e to carboplatin or vincristine in the induction phase is calculated including the rest periods (2 weeks). If subjects continued on to maintenance therapy, the last date of exposure in induction phase is the day before the start of maintenance therapy. If the subject does not continue on to maintenance therapy, the last date of exposure is calculated using the planned cycle duration, i.e. the last date of exposure is the date of first administration (of carboplatin or vincristine) in induction + 83 days. If the subject dies or if the data cutoff date is prior to the calculated date of last exposure, the date will be capped at the date of death or data cutoff. **Maintenance phase:**

Maintenance phase will continue for up to a total of 8 cycles, each cycle will be 6 weeks in duration and consists of 4 weekly doses of carboplatin followed by 2 weeks of rest, and three weekly doses of vincristine given concomitantly with the first 3 weeks of carboplatin , followed by three weeks of rest. The maintenance phase refers to the dosing after the first 12 weeks, and will be identified by having at least 9 non-zero doses of Carboplatin, or at least 11 non-zero doses of Vincristine. For Carboplatin/Vincristine, maintenance cycle week1 dates are defined by the following non-zero doses: dose 9/dose 11, dose 13/dose 14, dose 17/dose 17, dose 21/dose 20, dose 25/dose 23, dose 29/dose 26, dose 33/dose 29, and dose 37/dose 32, respectively.

The ***last date of exposur***e to carboplatin or vincristine in the induction phase is calculated including the rest periods (2 or 3 weeks). The last date of exposure is calculated using the planned cycle duration, i.e. the last date of exposure is the date of last week 1 administration (of carboplatin or vincristine) in maintenance + 41 days. If the subject dies or if the data cutoff date is prior to the calculated date of last exposure, the date will be capped at the date of death or data cutoff.The ***number of cycles*** of maintenance therapy will be determined as the following total number of non-zero doses:

- Carboplatin: 1 cycle – 9 to 12 doses; 2 cycles – 13-16 doses; 3 cycles – 17 to 20 doses; 4 cycles – 21 to 24 doses; 5 cycles – 25 to 28 doses; 6 cycles – 29 to 32 doses; 7 cycles – 33 to 36 cycles; 8 cycles – ≥ 37 doses.

- Vincristine: 1 cycle – 11 to 13 doses; 2 cycles – 14-16 doses; 3 cycles – 17 to 19 doses; 4 cycles – 20 to 22 doses; 5 cycles – 23 to 25 doses; 6 cycles – 26 to 28 doses; 7 cycles – 29 to 31 cycles; 8 cycles – ≥ 32 doses.

Duration of exposure to carboplatin and vincristine (days) will be calculated by treatment phase (induction and maintenance phase) and overall (if applicable) as:

Duration of [study drug] exposure (days) in induction phase = (Date of first week1 dose of [study drug] in maintenance – 1 day) - (date of first administration of [study drug]) + 1, for those who entered maintenance. For those who did not enter maintenance therapy, duration of maintenance will be defined as [minimum (date of first administration of [study drug] + 83 days, date of death, date of data cutoff) - (date of first administration of [study drug]) + 1.

Duration of [study drug] exposure (days) in maintenance phase = [minimum(Date of last week1 dose of [study drug] in maintenance + 41 days, date of death, date of data cutoff)] - (date of first week1 dose of [study drug] in maintenance) + 1.

Table 2-7 Definition of last date of exposure of study drug

Scenario	Definition of last date of exposure of study drug	Example
Carboplatin, Vincristine	The planned end date of the last cycle in which the last non-zero dose of the investigational drug was last administered (i.e. last week 1 date of administration + (planned interval duration of either induction or maintenance, as applicable))	Example 1: Subject discontinues during induction therapy. The last date of exposure is the first date of administration + 83 days.
	If carboplatin or vincristine was permanently discontinued during induction, set the last date of exposure equal to the planned end date of induction,	
	If carboplatin or vincristine was permanently discontinued during maintenance, set the last date of exposure equal to the planned end date of the last cycle. last week 1 administration date + 41 days,	Example 2: Subject discontinues during maintenance therapy after receiving the week 45 dose. The week 43 (C dose 29/V dose 26) dose date was 21Jan2021. The last date of exposure is the 21Jan2021 + 41 days = 03Mar2021.
	If carboplatin or vincristine was not permanently discontinued, set the last date of exposure equal to the data cut-off date.	Example 3: if Carboplatin or vincristine was not permanently discontinued prior to or on the data cut-off date, the last date of exposure is the data cut-off date.

Scenario	Definition of last date of exposure of study drug	Example
	Note: If the patient died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cut-off date, it should be truncated to the date of data cut-off.	
Dabrafenib, Trametinib	Date of last administration of a non-zero dose of the study drug.	Example 4: A patient had a permanent discontinuation of the study drug on 06Jan2016 after being put on a temporary interruption since 01Jan2016. In this case the last date of exposure is 31Dec2015.

Summary of duration of exposure to each combination partner will include categorical summaries based on clinically meaningful time intervals (8-<24, 24-<56, 56-<112, >= 112 (weeks)) and using descriptive statistics (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum) using appropriate units of time.

Cumulative dose and average daily dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment component, respectively. Average daily dose is defined as [Cumulative dose (dosing unit) / Number of dosing days]; drug free days are not counted as dosing days.

Cumulative dose and average daily dose will be summarized both in mg and mg/kg for dabrafenib and trametinib. Total actual cumulative dose (mg/kg) of dabrafenib and trametinib is calculated as the sum of the daily doses in mg/kg, where the mg/kg dose on any particular day is calculated as the dose in mg divided by the current weight (collected as per the visit schedule). Total actual cumulative dose (mg) of dabrafenib and trametinib is calculated as the sum of the daily doses in mg.

Cumulative dose and average dose per cycle will be summarized for mg/m^2 for carboplatin and vincristine. Total actual cumulative dose of carboplatin or vincristine is calculated as sum of cumulative dose.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of study drug administration. For dabrafenib and trametinib, the planned dose (mg) will be taken from the planned dose (mg) times the frequency from the first dosing record. Planned dose for carboplatin and vincristine is defined below. The planned cumulative dose will not be summarized/listed. It will be used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered over the duration for which the patient is on the study treatment as documented in the Dose Administration eCRF page.

For patients who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the patient is assumed to have taken a non-zero dose during dosing periods.

Dose intensity and relative dose intensity

Dose of dabrafenib and trametinib will be defined in the units of mg, and taken from the dose administration CRF. Dose of carboplatin and vincristine will be defined in units of mg/m^2, calculated as the administered dose received in mg/m^2 as taken from the dose administration CRF. **Dose intensity** (DI) for patients with non-zero duration of exposure is defined as follows:

DI (*unit of dose / unit of time*) = Actual Cumulative dose (*unit of dose*) / Duration of exposure to study treatment (*unit of time*).

For dabrafenib and trametinib, the unit of dose is mg and the unit of time is days; for carboplatin and vincristine, the unit of dose is mg/m^2 and the unit of time is weeks. [Note that for subjects < 12 kg in weight, the unit of dose for vincristine is mg/kg. If such subjects are enrolled in the study, their dosing data will be summarized separately.]

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (*unit of dose / unit of time)* = Planned Cumulative dose (*unit of dose*) / Duration of exposure (*unit of time*).

For carboplatin, the PDI is 116.67 mg/m^2/week, based on 6-week cycles with dosing of 175 mg/m^2 at weeks 1 to 4 only.

For vincristine, the PDI depends on the subject's weight and also on the treatment phase.

For subjects with weight ≥ 12 kg:

- during the induction phase, the PDI is 1.25 mg/m^2/week, based on 1.5 mg/m2 weekly *10 over 12 weeks.
- during the maintenance phase, the PDI is 0.75 mg/m^2/week, based on 1.5 mg/m2 weekly *3 over 6 weeks.

For subjects with weight < 12 kg:

- during the induction phase, PDI is 0.033 mg/kg/week , based on 0.05 mg/kg weekly *10 over 12 weeks.

- during the maintenance phase, the PDI 0.025 mg/kg/week, based on 0.05 mg/kg weekly *3 over 6 weeks.

Relative dose intensity (RDI) is defined as follows:

RDI (%) = [DI (*unit of dose / unit of time*) / PDI (*unit of dose / unit of time*)] x 100.

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components. DI and RDI will be summarized separately for induction and maintenance phase for carboplatin and vincristine.

Summary of RDI will include categorical summaries based on clinically meaningful intervals (<50%, 50-<75%, 75-<90%, 90-<110%, >=110%.)Note that for the purposes of DI and RDI derivation only for carboplatin and vincristine, the last date of exposure for the duration of exposure component of this calculation will not consider death date.

Table 2-8 Examples of dabrafenib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg) frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 05Jan2016	125 mg BID	250	No	No	
2	06Jan2016 / 03Feb2016	125 mg BID	200	Yes	No	AE
3	04Feb2016 / 25Feb2016	130 mg BID	260	Yes	No	As per protocol

Duration of exposure (days) = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 125*2*56 days = 14000 mg

Actual cumulative dose = 250*5 + 200*29 + 260*22 = 12770 mg

Dose intensity = 12770 mg / 56 days = 228.04 mg/day

Planned dose intensity = 14000 mg / 56 days = 250 mg/day

Relative dose intensity = DI / PDI = (228.04 mg/day) / (250 mg/day) = 91.2%

Table 2-9 Examples of trametinib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 10Jan2016	0.875 QD	0.875	No	No	

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
2	11Jan2016 / 15Jan2016	0.875 QD	0	Yes	No	AE
3	16Jan2016 / 25Feb2016	0.75 QD	0.75	Yes	No	AE

Duration of exposure = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 0.875*56 days = 49 mg

Actual cumulative dose = 0.875*10 + 0*5 + 0.75*41 = 39.5 mg

Dose intensity = 39.5 mg / 56 days = 0.705 mg/day

Planned dose intensity = 49 mg / 56 days = 0.875 mg/day

Relative dose intensity = DI / PDI = (0.705 mg/day) / (0.875 mg/day) = 80.6%

Table 2-10 Examples of carboplatin dose administration and exposure

Nominal Visit number	Start/End Date	Phase	Dose Prescribed (mg/m2), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
Week 1 Day 1	01Jan2016 / 01Jan2016	Induction	175 weekly	175	No	No	
Week 2 Day 1	08Jan2016 / 08Jan2016	Induction	175 weekly	0	Yes	No	AE
Week 3 Day 1	15Jan2016 / 15Jan2016	Induction	150 weekly	150	Yes	No	AE
Week 4 Day 1	22Jan2016 / 22Jan2016	Induction	175 weekly	175	No	No	
Week 7 Day 1	13Feb2016 / 13Feb 2016	Induction	175 weekly	175	No	No	
Week 8 Day 1	20Feb2016 / 20Feb2016	Induction	175 weekly	175	No	No	
Week 9 Day 1	28Feb2016 / 28Feb2016	Induction	175 weekly	175	No	No	
Week 10 Day 1	09Mar2016 / 09Mar 2016	Induction	175 weekly	175	No	No	
Week 13 Day 1	31Mar2016 / 31Mar2016	Maintenance C1	175 weekly	175	No	No	
Week 14 Day 1	08Apr2016 / 08Apr 2016	Maintenance C1	175 weekly	175	No	No	
Week 15 Day 1	15Apr2016 / 15Apr2016	Maintenance C1	175 weekly	175	No	No	

Nominal Visit number	Start/End Date	Phase	Dose Prescribed (mg/m2), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
Week 16 Day 1	22Apr2016 / 22Apr2016	Maintenance C1	175 weekly	175	No	No	
Week 19 Day 1	14May2016 /14May2016	Maintenance C2	175 weekly	175	No	No	
Week 20 Day 1	21May2016 /21May2016	Maintenance C2	175 weekly	175	No	No	
Week 21 Day 1	28May2016 /28May2016	Maintenance C2	175 weekly	175	No	No	
Week 22 Day 1	04Jun2016 / 04Jun2016	Maintenance C2	175 weekly	175	No	No	

Induction:

Duration of induction = [31Mar2016-1 = 30Mar2016] – 01Jan2016 + 1 = 90 days = 12.86 weeks

Planned dose intensity 116.67 mg/m2/week

Actual cumulative dose induction= 175*6 + 150*1 = 1200 mg/m2

Dose intensity induction = 1200 mg/m2 / 12.86 weeks = 93.3 mg/m2/week

Relative dose intensity induction = DI / PDI = (93.3 mg/m2/week) / (116.67 mg/m2/week) = 80%

Maintenance:

Duration of maintenance = [14May2016 +41=24Jun2016]– 31Mar2016 + 1 = 86 days = 12.29 weeks

Planned dose intensity 116.67 mg/m2/week

Actual cumulative dose maintenance = 175*8 = 1400 mg/m2

Dose intensity maintenance= 1400 mg/m2 / 12.29 weeks = 113.9 mg/m2/week

Relative dose intensity maintenance = DI / PDI = (113.9 mg/m2/week) / (116.67 mg/m2/week) = 97.6%

Table 2-11 Examples of vincristine dose administration and exposure for ≥ 12 kg

Nominal Visit number	Start/End Date	Phase	Dose Prescribed (mg/m2), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
Week 1 Day 1	01Jan2016 / 01Jan2016	Induction	1.5 weekly	1.5	No	No	
Week 2 Day 1	08Jan2016 / 08Jan2016	Induction	1.5 weekly	0	Yes	No	AE
Week 3 Day 1	15Jan2016 / 15Jan2016	Induction	1.0 weekly	1.0	Yes	No	AE
Week 4 Day 1	22Jan2016 / 22Jan2016	Induction	1.5 weekly	1.5	No	No	
Week 5 Day 1	28Jan2016 / 28Jan2016	Induction	1.5 weekly	1.5	No	No	
Week 6 Day 1	04Feb2016 / 04Feb2016	Induction	1.5 weekly	1.5	No	No	
Week 7 Day 1	13Feb2016 / 13Feb 2016	Induction	1.5 weekly	1.5	No	No	
Week 8 Day 1	20Feb2016 / 20Feb2016	Induction	1.5 weekly	1.5	No	No	
Week 9 Day 1	28Feb2016 / 28Feb2016	Induction	1.5 weekly	1.5	No	No	
Week 10 Day 1	09Mar2016 / 09Mar 2016	Induction	1.5 weekly	1.5	No	No	
Week 13 Day 1	31Mar2016 / 31Mar2016	Maintenance C1	1.5 weekly	1.5	No	No	
Week 14 Day 1	08Apr2016 / 08Apr 2016	Maintenance C1	1.5 weekly	1.5	No	No	
Week 15 Day 1	15Apr2016 / 15Apr2016	Maintenance C1	1.5 weekly	0	No	Yes	AE

Induction:

Duration of induction = [31Mar2016-1 = 30Mar2016] – 01Jan2016 + 1 = 90 days = 12.86 weeks

Planned dose intensity induction 1.25 mg/m2/week

Actual cumulative dose induction= 1.5*8 + 1.0*1 = 13 mg/m2

Dose intensity induction = 13 mg/m2 / 12.86 weeks = 1.01 mg/m2/week

Relative dose intensity induction = DI / PDI = (1.01 mg/m2/week) / (1.25 mg/m2/week) = 80.9%

Maintenance:

Duration of maintenance = [31Mar2016 +41=11May2016]– 31Mar2016 + 1 = 42 days = 6 weeks

Planned dose intensity maintenance 0.75 mg/m2/week

Actual cumulative dose maintenance = 1.5*2 + 0 *1 = 3 mg/m2

Dose intensity maintenance = 3 mg/m2 / 6 weeks = 0.5 mg/m2/week

Relative dose intensity maintenance = DI / PDI = 0.5 mg/m2/week) / (0.75 mg/m2/week) = 66.7%

Dose reductions, interruptions or permanent discontinuations

The number of patients who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose interrupted' and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions and permanent discontinuations, respectively. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this block of entries, then it will be counted as one interruption.

Dose Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

Missing data: If dose is recorded but regimen is missing or entered as 'none', it is assumed that the investigational drug was taken as per-protocol.

2.4.2 Prior, concomitant, on study and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized by treatment group for the FAS. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized and listed.

Anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

On study Radiotherapy and Surgery

As on study radiotherapy and surgeries are allowed after centrally confirmed radiologic progression of disease or at least a total of 36 months of treatment plus follow-up, whichever comes first.Surgeries and radiotherapies occurring on study will be listed only.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall and by treatment group by means of frequency counts and percentages using FAS. In addition, summaries will include best response to the regimen. Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD).

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Non-drug therapies and procedures starting after the start of study treatment will also be summarized by SOC and preferred term.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Concomitant medications that have the potential to impact some specific analyses (e.g. PK, efficacy or safety analyses) will be identified prior to database lock. Separate summaries of these concomitant medications will be produced using the appropriate analysis set (e.g. FAS for those potentially affecting efficacy. According to the study protocol, treatment with substances which are strong inhibitors, or inducers of CYP3A4/5 and CYP2C8, or antiretrovirals or herbal medicines or other anti-cancer or anti-investigational drugs should be avoided. However, some patients may take these substances during the treatment period so these concomitant medications will be selected via programming and tabulated and listed in the Clinical Study Report. Treatment with the prohibited substances mentioned above will be identified in the database as protocol deviations.

2.5 Analysis of the primary objective

The primary objective of the LGG cohort is to compare the antitumor activity of dabrafenib in combination with trametinib versus the carboplatin and vincristine, as measured by overall response rate (ORR) to study treatment by central independent review assessment using RANO criteria, in children and adolescent patients with BRAF V600 mutation positive LGG whose tumor is unresectable and who require treatment.

2.5.1 Primary endpoint

ORR is defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) according to RANO criteria (see Appendix 3 of the study protocol). ORR will be calculated based on the FAS using central independent review of tumor assessment data. Only tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. See Appendix 5.5 for primary estimand definition.

Best overall response

The BOR will be assessed based on reported responses across all evaluation time points. Both CR and PR must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met. The next scheduled assessment may be used for purposes of confirmation of response. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

BOR for each patient is determined from the sequence of overall responses according to the following rules, up to progression:

- CR = at least two determinations of CR at least 4 weeks apart before progression
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
- SD = requires at least one SD assessment (or better) determined at or beyond the second regularly scheduled tumor assessment (nominally week 16 i.e >= 105 days allowing for the ±1 week visit window) from randomization (and not qualifying for CR or PR).
- PD = progression after start of study treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD at or beyond the second regularly scheduled post-baseline tumor assessment or progression)

If a patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the BOR determination for the primary endpoint. Further anti-neoplastic therapies will be identified via protocol deviations or from the data collected on ‘Anti-neoplastic therapies since last date of study drug’ as appropriate.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis in the LGG cohort is the comparison of ORR based on independent review assessment between the two treatment arms. The following statistical hypothesis will be tested:

$H_{01}: ORR_t \leq ORR_c$ vs. $H_{A1}: ORR_t > ORR_c$

where ORR_t is the ORR in the Trametinib plus Dabrafenib arm and ORR_c is the ORR in the control arm (carboplatin with vincristine). The analysis to test these hypotheses and compare the two treatment groups will consist of a Mantel Haenszel chi-square test at one-sided 2.5% level of significance.

The primary efficacy analysis will be performed on the FAS.

ORR will be summarized using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs (Clopper and Pearson 1934). The Odds ratio (dabrafenib + trametinib vs carboplatin + vincristine) and it's 95% confidence interval will be determined by logistic regression. Note that there is a possibility that the confidence interval for the odds ratio from the logistic regression may be inconsistent with the primary test.

2.5.3 Handling of missing values/censoring/discontinuations

Patients with unknown or missing best overall response (BOR) will be counted as non-responders in the analysis of ORR. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the BOR must be "Unknown". For the computation of ORR, these patients will be included in the FAS and will be counted as 'non-responders'. If a subject is determined to have non-measurable disease only, then the category of response can be expanded to include non-CR/non-PD.

2.5.4 Supportive analyses

As sensitivity analysis, ORR will be calculated and summarized for patients from the Evaluable Set. ORR will be summarized using descriptive statistics (N, %) by treatment arm along with two-sided exact binomial 95% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413]. Further sensitivity analyses identifying possible outcome scenarios may be performed in the event of patients being randomized but not treated.

New anticancer therapy sensitivity analysis for ORR

The analyses of ORR will be repeated using a stricter ITT approach i.e including all response assessments irrespective of new anti-neoplastic therapy using the FAS. This analysis will only be performed if data permits.

Response evaluations recorded after the initiation of new anti-neoplastic therapy will be included in sensitivity analysis of ORR, (i.e. the occurrence of new anti-neoplastic therapy will be ignored for the analyses). The sensitivity analyses will be performed based on both the investigator and independent review assessments using the FAS. In the summary tables, this approach is referred as 'new anticancer therapy ORR sensitivity.

ORR based on radiographic response by independent review assessment

The analyses of ORR will be repeated based on radiographic response assessed by independent review by only incorporating the radiographic data which includes the lesion measurements from target lesions, non-target lesions, and new lesion per RANO. Clinical status data and corticosteroid use data will not be considered for the supportive analyses based on radiographic response. Waterfall plot will be presented for this analysis.

Waterfall graphs will be used to depict the anti-tumor activity for independent and investigator assessments. These plots will display the best percentage change from baseline in the sum of the products of perpendicular diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall graphs. Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. A patient with only such assessments will be represented by a special symbol (e.g. ✶) in the waterfall graph. Assessments with "unknown" target lesion response and assessments with unknown overall response will be denoted in the waterfall plots. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of patients with tumor shrinkage and tumor growth. Bars will have different fill patterns for all possible values of overall response. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-12.

Table 2-12 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
case	Target response	Overall lesion response	Include in waterfall?	Non-target response	New lesion?
1	CR/PR/SD	PD	Yes as a bar	PD	any
2	CR/PR/SD	PD	Yes as a bar	any	Yes
3	UNK	UNK or PD	Yes as an x	any	any
4	CR/PR/SD	UNK	Yes as a bar	UNK	No
5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
6	PD	PD	Yes as a bar	any	any

Additionally, swimmer plots of time to onset and duration of response based on independent and investigator review will be created for the FAS.

Concordance analysis of ORR

An assessment of the concordance between central independent reviewer assessment and local investigator assessment of the Best Overall Response for each patient will be provided. The calculation will be based on the percent agreement (the proportion of response outcomes that agree or match across both Independent Reviewer and Investigator Assessments).

Subgroup analysis for ORR

If the primary efficacy analysis is significant, the primary endpoint of ORR will be summarized for the subgroups specified in Section 2.2.1 based on the central independent reviewer assessment and using the same conventions as for the primary analysis. For each of the subgroups, proportion of patients with objective response and the two-sided exact 95% will be provided.

[redacted]

Reasons for "Unknown" BOR

Patients with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD and/or unconfirmed CR/PR only occurring prior to week 16 visit

2.6 Analysis of the key secondary objective

Not Applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are to:

- Evaluate ORR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by investigator review per RANO
- Evaluate duration of response (DOR) of dabrafenib in combination with trametinib versus carboplatin with vincristine by both investigator and central independent review per RANO
- Evaluate progression-free (PFS) survival of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review per RANO
- Evaluate time to response (TTR) of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review per RANO

- Evaluate CBR of dabrafenib in combination with trametinib versus carboplatin with vincristine, as measured by both investigator and central independent review per RANO
- Evaluate overall survival (OS) of dabrafenib in combination with trametinib versus carboplatin with vincristine

2.7.1 Secondary endpoints

A hierarchical approach will be taken to control for the overall type-I error rate for testing of multiple endpoints: PFS will be formally tested only if the primary endpoint ORR is statistically significant and then OS will be formally tested if PFS is also significant. PFS and OS will be formally tested at the time of primary analysis if ORR is significant. No other multiplicity adjustments are planned for secondary endpoints testing.

ORR by investigator review

The evaluation of ORR will be repeated by investigator review assessment as per RANO criteria based on the FAS and the Evaluable Set separately.

Duration of response

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to RANO criteria. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression per RANO or death due to any cause. If a patient has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, DOR will be censored at the date of the last adequate tumor evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier (see Section 2.7.3).

DOR will be analyzed as per investigator and central independent reviewer assessments separately. The analyses of DOR will be based on the FAS and will be repeated based on the Evaluable set.

Progression free survival

Progression free survival (PFS) is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be calculated using RANO criteria based on investigators and central independent review of tumor assessments separately. The analysis will include all data observed up-to the cut-off date. If a patient has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier. (See Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment). Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages without supporting evidence satisfying progression criteria per RANO will not be considered disease progression for PFS derivation. The analysis will be based on FAS and Evaluable Set separately.

Time to response

Time to response (CR or PR) is the time from date of randomization to first documented response of CR or PR (which must be confirmed subsequently) according to RANO criteria. All patients in the FAS will be included in the time to response calculation. Patients who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FPFV - LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other patients.

TTR will be analyzed using investigator and independent reviewer assessments separately.

Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of 24 weeks. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 23 weeks or later (i.e >= 161 days) from randomization, allowing for the ±1 week visit window for tumor assessments.

CBR will be analyzed using investigator and independent reviewer assessments separately. CBR will be calculated using the FAS set and Evaluable Set separately.

Overall Survival

Overall Survival (OS) is defined as the time from date of randomization to date of death due to any cause. A cut-off date will be established for each analysis of OS. All deaths occurring on or before the cut-off date in the FAS will be used in the OS analysis.

If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact (Section 2.1.1).

2.7.2 Statistical hypothesis, model, and method of analysis

[redacted]

Duration of response

DOR will be listed and summarized by treatment group for all patients in the FAS with confirmed BOR of CR or PR. The distribution of duration of response will be estimated using

the Kaplan-Meier method and the median duration of response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. No inferential analysis that compares duration of response between the two treatment groups will be performed. In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs [Kalbfleisch JD and Prentice RL. (2002)] at several time points (including at least 4, 6,12 and 18 months) will be summarized.

Progression Free Survival

The distribution of PFS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment group. The median and 25th and 75th percentiles of PFS along with 95% confidence intervals will be presented by treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, using a Cox model. In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at timepoints including 6, 12, 18, and 24 months will be summarized. Censoring reasons will also be summarized. A log-rank test at the one-sided 2.5% level of significance will be used to compare the two treatment groups. The PFS will be formally tested at the time of primary analysis.

Time to response

Time to response data will be listed and summarized by treatment group. The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. No inferential analysis that compares time to response between the two treatment arms will be performed. In addition, a responders-only analysis will also be performed using descriptive summary statistics.

Overall Survival

The survival distribution of OS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment group. The median and 25th and 75th percentiles of OS along with 95% confidence intervals will be presented by treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a Cox model. In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at timepoints including 6, 12, 18, and 24 months will be summarized. A log-rank test at the one-sided 2.5% level of significance will be used to compare the two treatment groups. The OS will be formally tested at the time of primary analysis.

2.7.3 Handling of missing values/censoring/discontinuations

DOR and PFS

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy, DOR and PFS will be censored at the date of the last adequate tumor before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of randomization will be used.

In particular, DOR and PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is administered; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-13 for censoring and event date options and outcomes for DOR and PFS.

Table 2-13 Outcome and event/censor dates for DOR and PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim*	Date of last adequate assessment	Censored
New anticancer therapy (including cancer related surgery and radiotherapy) given prior to	Date of last adequate assessment on or prior to	Censored

Situation	Date	Outcome
protocol defined progression (including patients who crossover from the control arm to the treatment arm)	starting new anti-cancer therapy	
Death before first PD assessment	Date of death	Event

* This refers to undocumented progression based on investigator claim only. Clinical Status will be considered as appropriate in the determination of progression per RANO criteria.

Censoring pattern of PFS

Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Initiation of new cancer therapy prior to progression
6: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments (see Section 2.7.3 for definition):

1. Analysis cut-off date,
2. Start date of further anti-neoplastic therapy,
3. Date of consent withdrawal,
4. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. ‘Ongoing’,
2. ‘New cancer therapy added’,
3. ‘Withdrew consent’,
4. ‘Lost to follow-up’,

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed. then the PFS censoring reason will always default to ‘Adequate assessment no longer available’. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than the interval of 2 missing tumor assessments then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced for PFS by investigator and central independent reviewers. The censoring patterns will be compared between investigator and central independent reviewers.

Clinical Benefit Rate

Patients with unknown or missing best overall response (BOR) will be counted as non-responders in the analysis of CBR.

OS

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date patient was alive, i.e., last contact date (see Section 2.1.1).

2.7.4 Supportive analyses

DOR, and PFS based on radiographic response by independent review assessment

The analyses of DOR, and PFS will be repeated based on radiographic response assessed by independent review by only incorporating the radiographic data which includes the lesion measurements from target lesions, non-target lesions, and new lesion per RANO. Clinical status data and corticosteroid use data will not be considered for the supportive analyses based on radiographic response.

New anticancer therapy sensitivity analysis for DOR and PFS

The analyses of DOR and PFS will be repeated using an ITT approach i.e including all response assessments irrespective of new anti-neoplastic therapy using the FAS.

Response evaluations and events (i.e. RANO documented disease progression or death) recorded after the initiation of new anti-neoplastic therapy will be included in sensitivity analyses of DOR and PFS, (i.e. the occurrence of new anti-neoplastic therapy will be ignored for the analyses). The sensitivity analyses will be performed based on both the investigator and independent review assessments using the FAS and using the same statistical methods for DOR and PFS described in Section 2.7.2. In the summary tables, this approach is referred as ‘new anticancer therapy DOR sensitivity analysis’ and ‘new anticancer therapy PFS sensitivity analysis’.

Corticosteroids use

The drug name, dose, reason, dosing frequency per interval, and dose intensity will be listed. The dose intensity is calculated as the cumulative dose divided by the duration of exposure per interval. Any corticosteroids use starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

2.8 Safety analyses

All safety analyses will be based on the safety set unless otherwise specified.

2.8.1 Adverse events (AEs)

Adverse events are coded using MedDRA terminology. The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class (SOC) will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational group (dabrafenib and trametinib).

The following adverse event summaries will be produced by treatment group: overview of adverse events and deaths (number and % of patients with any AE, treatment-related AE, SAE, fatal AE, AE leading to discontinuation, AE leading to dose reduction/interruption, AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose adjustment and/or interruption, leading to dose reduction, and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

For legal requirements of clinicaltrials.gov and EudraCT, two required tables for on-treatment adverse events which are not SAE's with an incidence greater than and equal to 5% and on-treatment SAE's and SAE's suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

2.8.1.1 Adverse events of special interest / grouping of AEs

All AE groupings for a clinical program are stored in the Compound Case Retrieval Strategy sheet (CRS) with clear versioning and reference to the MedDRA version used.

All AESI definitions or AE grouping need to be specified in the CRS. If a CRS update is necessary, the final version needs to be available in a reasonable time ahead of the DBL. The CRS version should be included in a footnote of the AESI tables.

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to dabrafenib and trametinib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

AESI for dabrafenib and trametinib are:

- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Hypertension
- Pyrexia
- Pre-Renal and intrinsic renal failure
- Uveitis
- New primary //secondary malignancy
- Hypersensitivity
- Hyperglycemia
- Venous thromboembolism
- Pancreatitis
- Neutropenia

Summaries of these AESIs will be provided by treatment group, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, fatal outcome, etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths including on-treatment and post-treatment deaths will be produced by system organ class and preferred term.

All deaths will be listed for the Safety set, post-treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.8.3 Laboratory data

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Data analysis

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of lab parameter values over time (baseline and selected on-treatment timepoints) should be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBIL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

Potential Hy's Law events are defined as those patients with occurrence of AST or ALT > 3xULN and TBL > 2xULN and missing ALP or ALP < 2xULN at any time during the on-treatment period. Note that the criteria relating to combined elevations of AST (or ALT) and TBL are based on the peak values at any post-baseline time for a subject.

For patients with abnormal ALT or AST baseline values, a clinically significant liver safety signal corresponding to Hy's law is defined by : [ALT or AST > 3xbaseline] OR [ALT or AST >8xULN], whichever is lower, combined with [TBIL >2xbaseline AND >2xULN].

A figure displaying time course of hepatic function tests (ALT, AST, TBL, ALP) in patients meeting Hy's criteria will be displayed in the Safety Set. Additonally, evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be produced to display ALT and AST values by TBL values in units of ULN.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

ECG Data analysis

Standard 12-lead ECGs including PR, QRS, QT, QTcF, and HR intervals will be obtained local for each patient during the study. ECG data will be read and interpreted locally.

The number and percentage of patients with notable ECG values will be presented by treatment group:

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

The normal range for HR is displayed in Table 2-14. The number and percentage of patients with notable values will be presented.

Table 2-14 Recommendation for normal heart rate per age group and gender

Age group	0-1 month	1-3 months	3-6 months	6-12 months	1-3 years	3-5 years	5-8 years	8-12 years	12-18 years
HR (bpm) Boys	(125, 190)	(125, 185)	(110, 165)	(105, 165)	(95, 155)	(75, 125)	(60, 115)	(55, 100)	(50, 100)
HR (bpm) Girls	(135, 215)	(125, 200)	(120, 190)	(105, 185)	(95, 180)	(80, 125)	(70, 115)	(60, 110)	(50, 100)

Data shown as upper limit of normal, lower limit of normal for HR= heart rate. Ref.: adapted from Rijnbeek et al. 2001.

The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. A listing of all ECG assessments will be produced and notable values will be flagged. A separate listing of only the patients with notable ECG values may also be produced. In the listings, the assessments collected during the post-treatment period will be flagged.

The denominator to calculate percentages for each category is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline ECG notable value is defined as a post-baseline value that meets the criterion post-baseline but did not meet the criterion at baseline.

For each ECG parameter, descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized. Descriptive statistics at worst post-baseline and changes from baseline to worst post-baseline will also be summarized separately.

For each of the QTc and QT intervals, shift tables based on notable parameter categories (<450, 450-<481, 481-<501, ≥501 ms) at baseline and the worst post-baseline value observed.

Frequency counts and percentages of patients with newly occurring post-baseline qualitative ECG abnormalities (morphology) will be summarized. The denominator to calculate percentages is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline qualitative ECG abnormality is defined as a post-baseline abnormal finding which was not present at baseline.

Patients with notable ECG interval values and newly occurring qualitative ECG abnormalities will be listed and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

ECHO Data handling

ECHO data will be analyzed based on local reported results. The summaries will include all ECHO assessments performed no later than 30 days after the last date of study drug. All ECHO assessments will be listed, and those collected later than 30 days after study drug discontinuation will be flagged in the listing.

The same modality (ECHO or MUGA) for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) should be used to follow a patient throughout the study. The absolute change from baseline values will not be calculated for any patients where the post-baseline value was determined by a cardiac scan modality that is different than the one used to determine baseline value.

ECHO Data analysis

Absolute change from baseline in LVEF will be summarized in the worst case post-baseline. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- No change or any increase
- Any decrease:
  - > 0 - <10% Decrease
  - 10 - <20% Decrease
  - ≥20% Decrease
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

ECHO assessments of LVEF will be listed for each patient including absolute change from baseline at each assessed time interval. The values of potential clinical importance will also be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters are being collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-145 below.

Table 2-15 Criteria for notably abnormal vital signs

	Clinically notable criteria			
Vital sign (unit)	High		Low	
Systolic blood pressure [mmHg]	≥ 95th percentile of the age and height group[1]		≤ 5th percentile of the age and height group[1]	
Diastolic blood pressure [mmHg]	≥ 95th percentile of the age and height group[1]		≤ 5th percentile of the age and height group[1]	
Body temperature [°C]	≥ 38.4°C		≤ 35.0°C	
Pulse rate [bpm][2]	12-18 months	> 140	12-18 months	< 103
	18-24 months	> 135	18-24 months	< 98
	2-3 years	> 128	2-3 years	< 92
	3-4 years	> 123	3-4 years	< 86
	4-6 years	> 117	4-6 years	< 81
	6-8 years	> 111	6-8 years	< 74
	8-12 years	> 103	8-12 years	< 67
	12-15 years	> 96	12-15 years	< 62
	≥ 15 years	> 92	≥ 15 years	< 58
Weight	increase from baseline[3] of ≥ 2 BMI-for-age percentile categories[4]		decrease from baseline[3] of ≥ 2 BMI-for-age percentile categories[4]	

bpm=beats per minute; CDC= Centers for Disease Controls and prevention; NHLBI= National Heart, Lung, and Blood Institute;

[1] Blood pressure percentiles are calculated for each blood BP record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

Note: Methods applies to patients less than 3 years old.

	Clinically notable criteria	
Vital sign (unit)	High	Low

[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; 377: 1011-18.

[3] Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to or greater than the 95th percentile);

[4] BMI-for-age percentiles categories (P3, P5, P15, P25, P50, P75, P85, P95, P97) are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/);

Note: For patients less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the recumbent length; for patients over 228 months- old, percentiles are not available and will be considered as missing.

The number and percentage of patients with notable vital sign values (high/low) will be presented by treatment group.

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP. Baseline is defined as the last non-missing value prior to or coinciding with first dose. The worst post-baseline value refers to the worst post-baseline value on treatment.

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure. For each parameter, only patients with a value at both baseline and post baseline (on treatment) will be included.

A listing of all vital sign assessments will be produced by and notable values will be flagged. A separate listing of only the patients with notable vital sign values may also be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Performance status

The Karnofsky and Lansky performance status scale (Table 2-16) will be used to assess physical health of patients:

Table 2-16 Performance status criteria

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be in multiples of 10			
Karnofsky (age ≥16 years of age)		**Lansky** (age <16 years)	
Score	**Description**	**Score**	**Description**
100	Normal, no complaints no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity, minor signs of symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort, some signs of symptoms of disease.	80	Active, but tires quickly.

70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play, keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.

Frequency counts and percentages of patients in the score category of 100, 90, 80, 70, and < 70 will be provided by time point based on the windows defined in Section 2.1.1. A summary of change from baseline by scheduled visits will be performed by treatment group, as well as the worst case post-baseline and the best case post-baseline changes during the study.

A supporting listing will also be provided.

2.8.4.4 Dermatological Evaluation

Skin examination results will be summarized by frequency counts and percentages of patients in each category (normal, abnormal) by scheduled time points by each treatment group. A supporting listing will also be provided.

[redacted]

.

2.8.4.7 Growth and development (Height and Weight)

Growth data consist of height, weight, BMI, height velocity and weight velocity.

Height and BMI will be summarized at 6-month intervals, using the standard deviation scores (SDS, also called z-score), velocity and velocity SDS. The relevant height and weight values for each 6-month period are defined using time windows, as defined in Table 5-3. The z-scores will allow identification of potential outliers.

The formula used to calculate the SDS and height and weight velocities are provided in the Appendix 5.3.2.

Note that BMI SDS are reported instead of weight SDS as no reference data for weight are provided by the WHO for age beyond 10.

Height and BMI SDS and height and weight velocity SDS will be summarized using descriptive statistics (mean, standard deviation, range) for each time window (at Baseline and thereafter allowing informal comparison of growth data), as well as by presenting number of patients with SDS values lower/higher than 5^{th}/95^{th} percentiles respectively.

Box plots will be plotted for each time window. A shift table to compare baseline SDS to the worst on-treatment SDS categorized as Low (SDS <- 1.645), High (SDS > 1.645) or Normal (-1.645 ≤ SDS ≤ 1.645) will be produced for height and BMI SDS. Another shift table to compare the baseline height SDS to the last available on-treatment height SDS categorized according to the main percentile lines (>95^{th}, 95^{th} to 90^{th}, 90^{th} to 75^{th}, 75^{th} to 50^{th}, 50^{th} to 25^{th}, 25^{th} to 10^{th}, 10^{th} to 5^{th} and ≤5^{th} percentile) will be produced. All height and BMI SDS, velocity and velocity SDS data will be listed, and values of SDS and velocity SDS outside of the central 95% of population values will be flagged as either High (SDS > 1.645) or Low (SDS < -1.645).

In addition, a mixed model will be used to estimate differences of change from baseline in height SDS between treatment groups. A mixed model with height SDS as the response variable and time, gender, and treatment as explanatory variables will be fit using PROC MIXED. See Appendix 5.4.5 for model specifications and further details.

2.8.4.8 Ophthalmologic exam

Visual acuity will be converted from snellen to logMAR scale as defined in Holladay 1997 (20), and categorized as the following change from baseline:

- Improvement: ≥ 0.2 logMAR improvement (decrease in logMAR)
- Stable: neither ≥ 0.2 logMAR improvement nor worsening, where
- Worsening: ≥ 0.2 logMAR worsening (increase in logMAR)

Visual acuity categories at each time point, as well as best and worst category on treatment will be presented. Further exploratory analyses of change in visual acuity may be performed. Data from ophthalmologic exams will be listed by treatment group.

[redacted]

2.8.4.10 Palatability

Data on palatability assessments for dabrafenib and trametinib oral solution (bitterness, sweetness, texture and overall taste) will be summarized and listed by treatment group.

2.8.4.11 Additional analyses

Time to first occurrence

Time to first occurrence of an event is defined as time from start of study treatment to the date of first occurrence of this event (or first event within an AE grouping), i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.

For Kaplan-Meier analyses of time to occurrence, in the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- new anticancer antineoplastic therapy start date
- end date of on-treatment period
- data cut-off date
- withdrawal of informed consent date.

Failure curves (ascending Kaplan-Meier curves) will be constructed. Median together with 95% confidence interval as well as 25th percentile and 75th percentile will be presented.

In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

2.9 Pharmacokinetic endpoints

All PK analyses will be performed based on the PAS unless otherwise specified.

PK parameters

For subjects where dense PK is collected on Day 15, the PK parameters that will be determined if data permit are shown in Table 2-17. For subjects where sparse PK is collected, Ctrough and Cmax may be reported if data permit. The PK parameters will be derived using non-compartmental methods using WinNonlin® software version 6.4.

Table 2-17 Non-compartmental PK parameters for dabrafenib and trametinib

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (ng*h/mL)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (ng*h/mL); tau= 12 hrs
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (h).
Ctrough	Measured concentration at the end of a dosing interval at steady state (taken directly before next administration) (ng/mL)The trough (predose) plasma concentration determined directly from the raw concentration-time data
Cavg	Steady state average plasma concentration (ng/mL)
Tlast	The last measurable concentration sampling time for the AUClast calculation (h)

Descriptive statistics (n, mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented for Pharmacokinetic analysis set for all dabrafenib (and its metabolites) and trametinib PK parameters defined in Table 2-17, except Tmax and Tlast, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed using the Full analysis set.

PK concentrations

Only valid PK concentrations will be used in the analyses as defined in Section 2.2.

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for dabrafenib, metabolites and trametinib concentrations will be presented by each scheduled time point and actual leading dose (i.e. the dose taken on the day prior to the PK sampling day) for the Pharmacokinetic analysis set. Zero concentrations will not be included in the geometric mean

calculation. Graphical presentation will be provided on mean concentration at each scheduled time point for PK sub-population where the full PK profile is available.

Individual concentration-time profiles for dabrafenib and trametinib concentrations with median will be displayed graphically by treatment for Full analysis set on the semi-log view. In addition, the mean (+/- SD) and geometric mean concentration-time profiles for dabrafenib (+ its metabolites) and trametinib over time will be displayed graphically for Pharmacokinetic analysis set on the linear and semi-log view.

All individual plasma dabrafenib metabolites and trametinib concentration data will be listed for the Full analysis set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

[redacted]

2.10 Patient-reported outcomes

Patient reported outcome (PRO) will only be evaluated for the LGG cohort. The FAS will be used for analyzing PRO data unless specified differently. One PRO questionnaire: the PROMIS Parent Proxy Global Health 7+2 will be used to evaluate the quality of life of patients between treatment groups. The 7+2 item parent proxy pediatric global health measure include a one global health score plus a single score from pain and a score from fatigue interference item which are scored independently. These two items are administered but do not contribute to the global health score. Rather, they are “signal” items that provide initial score estimates for pain interference and fatigue.

The PRO instruments are planned to be administered on Day 1, at Week 5 and every 8 weeks until Week 56, then every 16 weeks thereafter until disease progression per RANO criteria.

The baseline is defined as the last PRO assessment on or prior to randomization.

Compliance to the schedule of administration of PRO assessments will be summarized by treatment group, for baseline and post-baseline on treatment assessments and scheduled post-treatment time points. The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

1. yes
2. yes, fully completed
3. yes, partly completed
4. no, patient missed scheduled assessment visit
5. no, patient refused due to poor health
6. no, patient refused (unrelated to health)
7. no, study staff felt patient was too ill
8. no, questionnaire not available in appropriate language
9. no, institutional error
10. no, device not available
11. no, technical issues
12. no, other
13. no

A summary of the number and percentage of patients with questionnaire completion of 'yes' or 'no' (where categories 1-3 are counted as 'yes' and categories 4-13 are counted as 'no') will also be summarized by treatment group and time point.

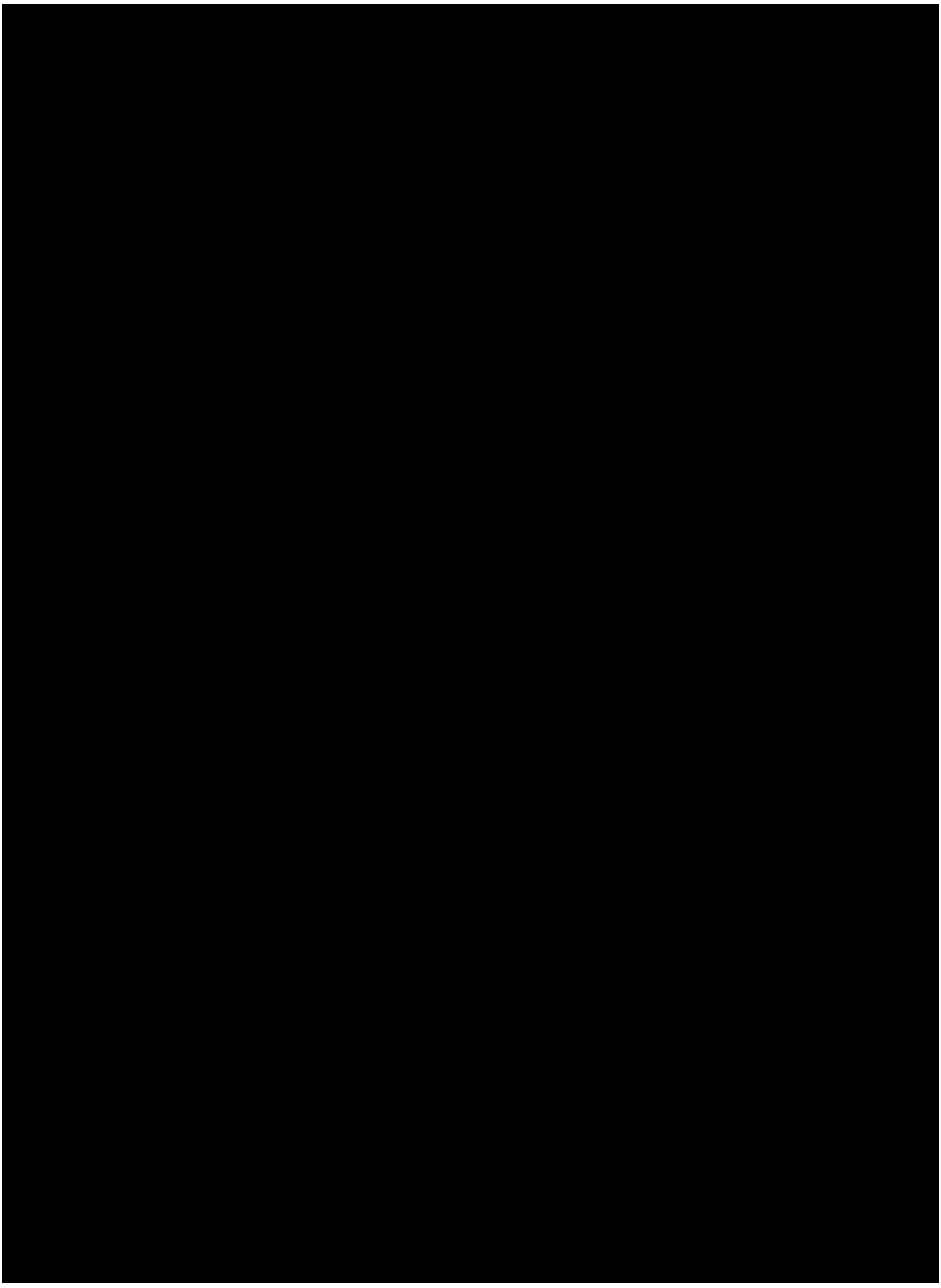
Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide [PROMIS global scoring manual, Christopher B. Forrest, 2013]. No imputation procedures will be applied for missing items or missing assessments.

Descriptive statistics will be used to summarize the scored scales of PROMIS Parent Proxy Global Health 7+2 at each scheduled assessment time point for each treatment group. Additionally, change from baseline in the scale at the time of each assessment will be summarized. Subjects with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

In addition, a repeated measures model for longitudinal data will be used to estimate differences in PROMIS Parent Proxy Global Health 7+2 scores between treatment groups. The modeling will be done on the actual score. Note that the modeling of the change in score or the actual score is equivalent since adjustment for baseline score is considered [CHMP Guideline on adjustment for baseline covariates 2015]. The repeated measures model will include terms for

fixed effects of treatment, visit, baseline value as main effects, and an interaction term for treatment by visit. The differences in least square means between the treatment groups and corresponding 95% confidence interval will be presented by visit. This analysis will be restricted to patients with an evaluable baseline score and at least one evaluable post-baseline score. All data collected until end of treatment (including the end of treatment assessment) will be included in the analysis. Note that only data collected under treatment (i.e. while the patient is treated) will be included. The end of treatment assessment will be included if collected within 30 days of the last dose intake.

As a first approach, an unstructured correlation matrix will be used to model the correlation within patients. The structure of the correlation matrix will be investigated and simplified using likelihood ratio tested if appropriate.



[redacted]

2.13 Interim analysis

No interim analysis is planned for the LGG cohort.

2.14 Crossover Phase

Baseline

Baseline is defined as the most recent non-missing value before the first dose of study treatment (dabrafenib plus trametinib) on the crossover treatment period. Baseline values will be established prior to the start of the crossover phase.

Response will be determined separately for the randomized phase and the crossover phase. Baseline lesion assessments will be re-established prior to initiation of crossover therapy and response will be calculated based on the appropriate baseline for each respective phase.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: up to 90 days prior to the first dose on the crossover phase
2. ***on-treatment period***: from date of first administration of crossover study treatment to 30 days after date of last actual administration of study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of crossover study treatment.

The reference date for both efficacy and safety measures in the Crossover phase is the date of first dose of dabrafenib plus trametinib on the crossover treatment period.

The tables and listings for the randomized and crossover phases will be separate.
Note: Analyses specified as for the Randomized phase will only include data prior to crossover except for analyses of overall survival (OS). Similarly analyses specified for the crossover phase will only use data from after the date of crossover.

Only key summary tables will be provided for the crossover phase for example; disposition, treatment discontinuation, exposure, deaths, AE/SAEs, ORR, and time to response. Listings will be provided for the crossover data.

3 Sample size calculation

3.1 Primary analysis

To detect a 30% improvement in ORR based on central independent review response of 50% in the dabrafenib plus trametinib arm vs 20% in the carboplatin with vincristine arm (Lassaletta 2017 JCO) with at least 80% power, 102 patients are required to be randomized in the two treatment arms in a 2:1 ratio based on using a Maentel-Haenszel chi-squared test and one-sided alpha = 2.5%.

Based on the following assumptions i.e 102 patients, 2:1 randomization ratio between the two treatment arms, Maentel-Haenszel chi-squared test and one sided alpha of 2.5%, the study power scenarios under different true ORR are shown in Table 3-1.

Table 3-1 Power scenarios under different true ORR in BRAF V600 mutant LGG

True ORR % (carboplatin with vincristine arm vs. dabrafenib plus trametinib)	Power (%)
20% vs. 55%	90%
20% vs. 50%	80%
20% vs. 45%	67%
15% vs. 50%	90%
25% vs. 50%	66%

3.2 Power for analysis of key secondary variables

Not applicable.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of date of last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year (yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of that specific record, if the imputed date is < start date of that record:

Use the start date of that record

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications, and for assigning pre/on/post treatment periods.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at

that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as ‘<X’ (i.e. below limit of detection) or ‘>X’, prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.3.1 Growth data

SDS will be calculated using the current formulae provided by the WHO as follows:

1. Calculate $z_{ind} = \frac{\left(\frac{X}{M}\right)^{L} - 1}{LS}$
2. If $|z_{ind}| \leq 3$, $SDS = z_{ind}$
   If $z_{ind} > 3$, $SDS = 3 + (X - SD3pos) / SD23pos$
   If $z_{ind} < -3$, $SDS = -3 + (X - SD3neg) / SD23neg$

where:

- *X* is height in centimeters or BMI in kilograms/m^2,
- *L*, *M* and *S* are height or BMI-, sex- and age-specific reference values from the WHO Growth Charts.
- SD3*pos* is the cutoff 3SD calculated by the LMS method:
  $SD3pos = M * (1 + LS*3)^{1/L}$
- SD3*neg* is the cutoff -3SD calculated by the LMS method:
  $SD3neg = M * (1 + LS*(-3))^{1/L}$
- SD23*pos* if the difference between the cutoffs 3SD and 2SD:
  $SD23pos = M * (1 + LS*3)^{1/L} - M * (1 + LS*2)^{1/L}$
- SD23*neg* if the difference between the cutoffs -2SD and -3SD:
  $SD23neg = M * (1 + LS*(-2))^{1/L} - M * (1 + LS*(-3))^{1/L}$

Height-for-age and BMI-for-age L, M and S reference values for males and females are available under http://www.who.int/childgrowth/standards/en/ (for patients aged between 0 to 5 years old) and http://www.who.int/growthref/en/ (for patients aged between 5 to 19 years old). These correspond to the latest available international references available at this time and described in the 2007 Bulletin of the World Health Organization (Mercedes de Onis et al 2007). The age category immediately above the patient's exact age should be used. SDS is actually a

Z score that measures the distance from the population mean in units of standard deviations. That is, SDS < 0 refers to values lower than the population mean, and for example SDS ≤ -1.645 refers to values in the lowest 5%. (The usual percentiles most commonly used in the clinical practice can be derived from the z-score by a normal distribution).

Note that BMI is reported instead of weight as no reference data are provided by the WHO for age beyond 10.

Height velocity is defined as follows:

Height velocity (cm/6-months) = (height in time window *k* – height in time window *k-1*) ÷ ([assessment date in time window *k* – assessment date in time window *k-1*] x [365.25/2]),

and similarly for weight velocity.

Velocity SDS is calculated as (velocity – mean) / SD, where mean and SD are obtained as the height-, weight-, sex- and age-specific values (Baumgartner et al 1986), where the age category immediately above the patient's exact age (at the assessment date in time window *k*) should be used. Velocity SDS will only be calculated for time window *k* if data also exists for time window *k-1*, since calculating across multiple units of 6 months requires more than one reference value to be taken into account.

Table 5-3 summarizes the time windows for growth data, where windows are centered at every 6 months after start of study treatment. Although height and weight are collected more frequently than every 6 months (post-enrollment), this choice of time window length was made to reflect the degree of accuracy in the reference values (every 6 months) that will be used in the calculation of summary variables of growth.
In case of multiple assessments falling into the time window interval, the closest to the target date will be considered. For example, If we have 3 assessments falling under the time window of Day 85 to 252, then the closest one to target day of 168 will be considered. If two assessments are equidistant from target date, the average will be considered of those respective assessments.

Table 5-3 Time windows for growth data (height SDS, height velocity, weight velocity, BMI SDS)

Planned assessment	Time window
Baseline	Days ≤1
Month 6 (Day 168)	Days 85 – 252
Month 12 (Day 336)	Days 253 – 420
Month 18 (Day 504)	Days 421 – 588
Month xx (Day xx * 28)	Days ((xx – 3) * 28 + 1) – Day ((xx + 3) * 28)
Day 1 = date of first intake of study drug xx = Every 6 months	

5.3.2 Bone Age

Bone age SDS will be calculated as (bone age – chronological age) / SD) where the chronological age is the age in months at the time of the X-ray evaluation and SD is the sex- and age-specific standard deviation, as defined in the table below:

Table 5-4 Variability in Bone Age

Chronologic Age in Months	Boys SD	Girls SD
12	2.1	2.7
18	2.7	3.4
24	4	4
30	5.4	4.8
36	6	5.6
42	6.6	5.5
48	7	7.2
54	7.8	8
60	8.4	8.6
66	9.1	8.9
72	9.3	9
84	10.1	8.3
96	10.8	8.8
108	11	9.3
120	11.4	10.8
132	10.5	12.3
144	10.4	14
156	11.1	14.6
168	12	12.6
180	14	11.2
192	15	15
204	15.4	15.4

If the chronologic age falls between two values in the table above, the closest age should be used. If the chronologic age falls exactly in the middle between 2 values in the table above, then the age above the chronologic age should be used.

Table 5-5 Time windows for bone age SDS data

Planned assessment	Time window
Baseline	Days ≤ 1
Month 6 (Day 168)	Days 85 – 252
Month 12 (Day 336)	Days 253 – 420
Month 18 (Day 504)	Days 421 – 588
Month xx (Day xx * 28)	Days ((xx – 3) * 28 + 1) – Day ((xx + 3) * 28)
Day 1 = date of first intake of study drug xx = Every 12 months	

5.4 Statistical models

5.4.1 Primary analysis

The null hypothesis of equality of response rate in the two treatment arm will be tested against one-sided alternative. The statistical hypotheses are:

$H_{01}: ORR_t \leq ORR_c$ vs. $H_{A1}: ORR_t > ORR_c$

where ORR_t is the ORR in the Trametinib plus Dabrafenib arm and ORR_c is the ORR in the control arm (carboplatin with vincristine).

The Mantel-Haenszel chi-square test X^2_{MH} (implemented via SAS procedure FREQ with CMH option in the TABLES statement) will be used to test the difference in response rates between the treatment arms at one-sided 2.5% level of significance. The p-value corresponding to the CMH test for "general association" will be used which follows a Chi-square distribution with one degree of freedom.

If the sampling assumptions for chi-square test is not met, Fisher's exact test (implemented via SAS procedure FREQ with EXACT option in the TABLES statement) will be used to test the difference in response rates between the treatment arms. The rule for determining adequate sample size for $X^2$is that expected values should exceed 5 for all of the table cells.

Multiplicity adjustment

A hierarchical approach will be taken to control for the overall type-I error rate for testing of multiple endpoints: PFS will be formally tested only if the primary endpoint ORR is statistically significant and then OS will be formally tested if PFS is also significant. No other multiplicity adjustments are planned for secondary endpoints testing.

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Secondary efficacy analysis

Kaplan-Meier estimates

To analyze time to event endpoints (TTR, DOR, PFS and OS). An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. The TIME statement will include a variable with survival times and a (right) censoring variable with a value of 1, representing censoring. Kaplan-Meier survival and failure function estimates from this procedure will be used to construct the Kaplan-Meier figures.

Median survival will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer R and Crowley J. (1982)]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated

using Greenwood's formula [Collet D (1994).].

Hazard ratio

Hazard ratio will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).
An unadjusted Cox model will be used, i.e. the MODEL statement will include the treatment group variable as the only covariate.

Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

5.4.4 Implementation of RANO guidelines (protocol Appendix 3)

As described in the protocol, the ORR will be evaluated by RANO criteria for solid tumors. This section provides some details on how to derive these endpoints by RANO and further details are included in the protocol Appendix 3.

The RANO criteria for assessment of LGG differs from that for HGG primarily in that LGG assessments utilize T2/FLAIR imaging rather than contrast enhancement as these tumors rarely enhance while HGG assessments utilize Gadolinium enhanced imaging. LGG cohorts will be assessed per LGG modification of RANO criteria with the exception that minor response will not be evaluated as per protocol.

The major differences between RECIST 1.1 and RANO include:

- The measurability criteria for target lesion by RANO is based on two dimensions i.e two perpendicular diameters are measured for each target lesion;
- Corticosteroids use and clinical status are also considered for determining overall response;
- T2/FLAIR will be used for both measurable and non-measurable disease

Overall Lesion Response Collected on RANO eCRF page

In this study, Independent reviewer reported overall response and Investigator reported overall lesion response will be used for primary and secondary endpoints.

For investigator, the overall response by RANO will be derived based on the collected overall lesion response on eCRF page "RANO Overall Lesion Response" (ZR domain, ZRCAT = "RESPONSE ASSESSMENT IN NEURO-ONCOLOGY", and ZRSCAT = "OVERALL LESION RESPONSE").

For independent reviewer, the overall response by RANO will be derived based on the collected overall lesion response on eCRF page "RANO Overall Lesion Response" (ZR domain, ZRCAT

= ”RESPONSE ASSESSMENT IN NEURO-ONCOLOGY”, and ZRSCAT = ”OVERALL RESPONSE”).

There will be two evaluations at a given assessment for independent reviewer i.e. primary RANO radiologic review without clinical data (read 1 – ZREVAL = “PRIMARY REVIEW”) and a secondary RANO review with clinical data (read 2 – ZREVAL = “SECONDARY REVIEW”). Secondary RANO review (read 2) with clinical data will be used for the primary endpoint of Best overall response per independent review. Primary review (read 1) will be used in supportive analyses based on radiographic review only, without clinical data.

Calculation of Overall Lesion Response by RANO

Overall lesion responses by RANO are also calculated from the following components:

1. Target lesion measurements;
2. Non-target lesion response;
3. New lesion present (Yes/No);
4. Corticosteroids use;
5. Clinical status.

All these components are collected on the following eCRF pages:

1. RANO target lesion - Measurable enhancing lesion (T1) (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”MEASURABLE T2/FLAIR”);
2. RANO non-target lesion - Non-measurable enhancing lesion (T1) (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ” NON-MEASURABLE T2/FLAIR”);
3. RANO New Lesion (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”NEW”);
4. Corticosteroids use and clinical status are collected on the Modified RANO Assessment (ZR domain, ZRCAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”RESPONSE ASSESSMENT”).

All the above components are collected on the same eCRF pages for independent reviewer with the exception of ZICAT = ” RESPONSE ASSESSMENT IN NEURO-ONCOLOGY”.

Each target lesion by RANO criteria has two perpendicular diameters collected. In order to calculate the target lesion response, the product of the two perpendicular diameters is calculated for each target lesion. Then the sum of the products of diameters of all target lesions is compared to the baseline or nadir to determine the target lesion response.

The non-target lesion response is collected on the field of “Non-target lesion present” in the Modified RANO Assessment page, and is evaluated based on both non-target lesion eCRF

pages as shown above. However, no derivation will be performed from individual non-target lesion status to non-target lesion response.

The RANO response/progression criteria are summarized in Table 4-4.

Table 5-6 Summary of the RANO response criteria

	CR	PR	SD	PD
T2/FLAIR	None	≥50% decrease from baseline	<50% decrease from baseline but <25% increase from nadir	≥25% increase from nadir*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA**
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Worsened*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

*: Progression occurs when this criterion is met

**: Not Applicable (NA): Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

Note: The minor response category will not be utilized in this study.

Two fields in the Modified RANO Assessment page will not be used for any data analysis in the study: "New enhancement outside radiation field?", "Tumor present in histopathology".

5.4.5 Mixed Model for Height SDS

A mixed model will be used to estimate differences of change from baseline in height SDS between treatment groups. A mixed model with height SDS as the response variable and time, gender, and treatment as explanatory variables will be fit using PROC MIXED.

Two copies of visit number in integer (AVISITN) will be used to proxy the time of measurements. One copy of the time measure AVISITN is created and named TIME to specify the model with a continuous time measure (used for fixed effects) and the other named MONTH to specify the model with a categorical time measure (used for random effects).

In this model, as a first approach, a mixed model with an unstructured variance-covariance matrix will be used to model the correlation within patients. The structure of the correlation matrix and the use of random intercept will be further investigated if the first approach fails to converge. Therefore, we proposed the following sequence of model fits:

1. Step 1: Repeated measures with an unstructured variance-covariance matrix.
2. If it fails to converge, try the random intercept model with a AR(1) variance-covariance matrix for the repeated measures.

Below are the SAS codes for reference.

FIT 1

```
PROC MIXED DATA=SCC METHOD=REML;
        CLASS TRT01AN USUBJID MONTH SEXN;
        MODEL AVAL=TRT01AN TIME TRT01AN*TIME SEXN / SOLUTION DDFM=KENWARDROGER;
        REPEATED MONTH / SUBJECT=USUBJID TYPE=UN;
        ESTIMATE 'slope TRT D+T' TIME 1 TIME*TRT01AN 1 0;
        ESTIMATE 'slope TRT C+V' TIME 1 TIME*TRT01AN 0 1;
        ESTIMATE 'slope (D+T) - (C+V)' TIME*TRT01AN 1 -1;
         LSMEANS TRT01AN / PDIFF CL;
        RUN;
```

FIT 2

```
PROC MIXED DATA=SCC METHOD=REML;
        CLASS TRT01AN USUBJID MONTH SEXN;
        MODEL AVAL=TRT01AN TIME TRT01AN*TIME SEXN / SOLUTION DDFM=KENWARDROGER;
        RANDOM INTERCEPT / SUBJECT=USUBJID;
        REPEATED MONTH / SUBJECT=USUBJID TYPE=AR(1);
        ESTIMATE 'slope TRT D+T' TIME 1 TIME*TRT01AN 1 0;
        ESTIMATE 'slope TRT C+V' TIME 1 TIME*TRT01AN 0 1;
        ESTIMATE 'slope (D+T) - (C+V)' TIME*TRT01AN 1 -1;
         LSMEANS TRT01AN / PDIFF CL;
        RUN;
```

5.5 Estimands

5.5.1 Primary estimand for the primary objective

The primary clinical question of interest is: what is the relative effect of the two treatment strategies in increasing the ORR by independent review as per RANO criteria in children and adolescent subjects with BRAFV600 mutant LGG with progressive disease, regardless of study treatment discontinuation and before start of any new anti-neoplastic therapy.

The justification for the primary estimand is that it will capture the treatment effect of the study drug even after treatment is discontinued, but avoid potential confounding effects of any other new anti-neoplastic therapy.

The primary estimand is characterized by the following attributes:

1. Population: all subjects randomized with BRAFV600 mutant LGG with 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 details on the population are provided in protocol Section 5.
2. Primary Variable: BOR by independent review as per RANO criteria.
3. Treatment: the randomized treatment (the investigational treatment dabrafenib plus trametinib or the control treatment vincristine plus carboplatin), regardless of treatment discontinuation.

Handling of intercurrent events:

- **Discontinuation of study treatment for any reason:** Per treatment policy strategy, tumor assessment data collected after discontinuation of study treatment for any reason will be used to derive BOR. This includes subjects who were randomized but not treated.
- **Start of new anti-neoplastic therapy**: Per while on treatment strategy, tumor assessments collected before start of new anti-neoplastic therapy will be used to derive BOR. Tumor assessments collected on/after the start of new therapy will not be considered for evaluation of BOR.

Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria between the treatment arms as assessed by the Mantel-Haenszel chi-squared test. See sections 2.5.2 for details.

Sensitivity analyses for primary endpoint/estimand will be performed using the evaluable set, with all other aspects of the estimand as defined above. Additionally, analyses with response as assessed by the investigator (instead of by central review) will be done under the same estimand attributes.

5.5.2 Handling of missing values not related to intercurrent event

Subjects in FAS with unknown or missing BOR will be noted as such in the appropriate tables/listings and counted as non-responders in the analysis of ORR. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be "Unknown". If no valid post-baseline tumor assessments are available, the best overall response must be "unknown" unless progression is reported.

For the purpose of primary analysis, subjects with a BOR of "unknown" (UNK) will be treated as non-responders in estimating the ORR in the FAS.

5.5.3 Supplementary analysis

A supplementary analysis for the primary estimand will be done as defined below:

1. Population: all subjects randomized with BRAFV600 mutant LGG with 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 details on the population are provided in protocol Section 5.
2. Treatment: the randomized treatment (the investigational treatment dabrafenib plus trametinib or the control treatment vincristine plus carboplatin), regardless of treatment discontinuation or start of new anti-neoplastic therapy.
3. Variable: BOR by independent review as per RANO criteria.
    - Handling of intercurrent events:**Discontinuation of study treatment for any reason** - Per treatment policy strategy, tumor assessment data collected after discontinuation of study treatment for any reason will be used to derive BOR. This includes subjects who were randomized but not treated.

Start of new anti-neoplastic therapy- Per treatment policy strategy, tumor assessment data collected after start of anti-neoplastic therapy will be used to derive BOR.Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria between the treatment arms.

6 Reference

1. American Academy of Pediatrics. (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics, 114, 555-76.
2. Brookmeyer R and Crowley J. (1982) A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
3. CHMP guideline on adjustments for baseline covariates in clinical trials (2015)
   http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184923.pdf
4. Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
5. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
6. Christopher B. Forrest, et al. (2013), Development of the PROMIS_ pediatric global health (PGH-7) measure
7. Fleming S, Thompson M, Stevens R, et al. (2011) Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 377: 1011-18.
8. Hummel TR., Wagner L, Ahern C., et al. (2013) A pediatric phase 1 trial of vorinostat and temozolomide in relapsed or refractory primary brain or spinal cord tumors: a children's oncology group phase 1 consortium study. Pediatr. Blood Cancer. 60: 1452-7.
9. Kalbfleisch JD and Prentice RL. (2002) The Statistical Analysis of Failure Time Data. Wiley Series in Probability and Statistics.
10. Lashford LS, Thiesse P, Jouvet A, et al. (2002) Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J. Clin Oncol. 24:4684-91
11. Lassaletta A, Zapotocky M, Mistry M, et al. (2017). Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. J. Clin Oncol. 35(25): 2934-2941.
12. Neuenschwander B, Branson M and Gsponer T. (2008) Critical aspects of the Bayesian approach to Phase I cancer trials. Statistics in Medicine, 27, 2420-2439.
13. Nicholson HS, Kretschmar CS, Krailo M, et al. (2007) Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer. 110:1542–1550.
14. PROMIS global scoring manual, www.HealthMeasures.net.
15. Rijnbeek PR, Witsenburg M, Schrama E, et al. (2001) New normal limits for the paediatric electrocardiogram. Eur Heart J. 22: 702-11.
16. Ruggiero A, Cefalo G, Garre ML, et al. (2006) Phase II trial of temozolomide in children with recurrent high-grade glioma. J Neurooncol. 77:89-94
17. Smith B, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT and Forgue ST. (2000) Confidence Interval Criteria for Assessment of Dose Proportionality. Pharmaceutical Research, 17(10), 1278-83.

18. Warren KE, Gururangan S, Geyer JR, et al. (2012) A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: a Pediatric Brain Tumor Consortium study. J. Neurooncol.106: 643–649.
19. World Health Organization (WHO) Multicentre Growth Reference Study Group. (2009) WHO Child Growth Standards: Growth velocity based on weight, length and head circumference: Methods and development. Geneva: World Health Organization, http://www.who.int/childgrowth/en/.
20. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg. 1997;13:388-391.

NOVARTIS

Clinical Development

DRB436/Dabrafenib, TMT212/Trametinib

CDRB436G2201 / NCT02684058

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)

Statistical Analysis Plan (SAP) for HGG cohort- Amendment 2

Author:	Trial Statistician
Document type:	SAP Documentation
Document status:	Final
Release date:	30-Sep-2021
Number of pages:	67

Document History – Changes compared to previous final version of SAP

Version	Date	Changes
Final 1.0	11-Aug-2017	Initial final RAP Module 6
Amendment 1	26-Sep-2018	Changes to SAP amendment 1 - Section 1, description of LGG cohort is added - Section 1.1, updated the study design language to mention the LGG cohort. Added IDMC for the study - Section 1.2, added two new objectives/endpoints i.e Clinical benefit rate and palatability. [redacted] The primary endpoint is updated to central independent reviewer as per FDA feedback. This update has been made throughout the document. - Section 2.1.1, removed the baseline calculation for lab parameter “creatinine” as the study does not allow multiple assessment at screening. Corrected the typo for planned Visit timings for week 8 day 1 in Table 2-1, and 2-2 - Section 2.2, Clarified the definition of evaluable set - Section 2.2.1, added a safety subgroup analysis of AE related to study drug. - Section 2.3.1, added number of treated patients in the disposition summary - Section 2.4.2, added details for on study radiotherapy and surgery. Added best response to regimen for post antineoplastic therapies - Section 2.5.4, added new sensitivity analysis for ORR - Section 2.7.1, Moved PFS up in the order - Section 2.7.4, added waterfall plot for the supportive analysis - Section 2.8.1, clarified and added two tables as per ClinicalTrials.gov and Eudra CT - Section 2.8.1.1, added AESI - Section 2.9, clarified the PK sample collection - [redacted]
Amendment 2	01-May-2021	Changes to SAP amendment 2, updated based on protocol verion 5 - Section 1.2, updated language to match protocol version 5 - Section 2.1.1, clarified baseline for ECG, and added visit windows for additional safety parameters - Section 2.2, Evaluable set patient classification adjusted to correctly identify evaluable patients.

Version	Date	Changes
		- Section 2.2.1, added age subgroups for exposure summaries. - Section 2.4.1, updated calculations of dose intensity based on the planned dose at first dose to align with program definitions. - Section 2.5.1, clarified BOR is up to progression, and added number of days to clearly define 16 week SD requirement. - Section 2.5.4, removed subgroup analysis as it will be done at final analysis. - Section 2.7.2, updated time points for DOR, and added summary method for CBR. - Section 2.7.4, clarified waterfall plot presentation and removed graphical presentations of corticosteroids. - Section 2.8.1.1, updated AESI to current list of AESIs. - Section 2.8.3, updated Hy's law language to reflect new guidance. - Section 2.8.4.2, clarified height definition for subjects under age 2. - Section 2.8.4.4, dermatologic summary categories labels were removed. - Section 2.8.4.5, age of early puberty updated, analysis details added. - Section 2.8.4.6, bone age SDS calculation definition added. - Section 2.8.4.7, growth and development definitions and analyses added. - Section 2.8.4.8, visual acuity change over time analysis added. - Section 2.8.4.11, added definitions for censoring for time to first occurrence of AESI. - Section 2.9, added PK parameters Cavg and Tlast. - [redacted] - [redacted] - Section 2.12.2, added definition for duration of follow-up. - Appendix 5.3.1, Growth data calculation details added. - Appendix 5.3.2, Bone age SDS calculation and variability details added. - Appendix 5.4.4, details of RANO guidelines and identification of response from datasets defined. - Appendix 5.5, estimand language added.

Table of contents

List of abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
b.i.d.	*bis in diem*/twice a day
C_{avg}	Average Concentration
[redacted]	[redacted]
Cmax	The observed maximum (peak) plasma concentration after drug administration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CRP	C reactive protein
CSP	Clinical Study Protocol
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Event
DILI	Drug-induced liver injury
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
EBV	Epstein-Barr virus
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms for EDC
ECHO	Echocardiogram
EDC	Electronic Data Capture
EMA	The European Medicines Agency
eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBM	Glioblastoma multiforme
HSV	Herpes simplex virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGG	High Grade Glioma
HPMC	Hydroxypropylmethyl cellulose
i.v.	intravenous(ly)
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
Kg	Kilogram
LFT	Liver Function Test
LGG	Low Grade Glioma
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NSCLC	Non-small cell lung cancer
o.d.	*omnia die*/once a day
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic analysis set
PD	Progression of disease
p.o.	*per os*/by mouth/orally
PFS	Progression Free Survival
PK	Pharmacokinetics
POS	Probability of Success
PPS	Per-Protocol Set
PTC	Papillary thyroid cancer
PXA	Pleomorphic Xanthoastrocytoma
QT	Q to T interval (ECG)
QTcF	QT interval corrected using Fridericia method
RANO	Response Assessment in Neuro-Oncology Criteria
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
R Value	ALT/ALP in x ULN
SC	Steering Committee
SDS	Standard Deviation Score
SOC	Standard of Care
SOP	Standard Operating Procedure
TBIL	Total bilirubin
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CDRB436G2201, a multi-center, global, single arm, open-label, Phase II study conducted in children and adolescent patients with BRAF V600 mutation positive, (a) Low Grade Glioma (LGG), or (b) refractory or relapsed High Grade Glioma (HGG) after having received at least one previous standard therapy. This SAP will be used for the interim analysis, primary analysis, and final analysis for HGG cohort. All planned analyses for the LGG cohort are described in a separate analysis plan.

The content of this SAP is based on protocol CDRB436G2201 amendment version 05. All decisions regarding interim, primary and final analyses, as defined in the SAP document, have been made prior to database lock.

1.1 Study design

This study combines two pediatric glioma cohorts (HGG and LGG) into a single multi-center, open-label, phase II study.

The HGG cohort is a multi-center, single arm, open-label, Phase II study conducted in children and adolescent patients with BRAF mutation positive, refractory or relapsed HGG tumors after having received at least one previous standard therapy. BRAF V600 mutation-positive tumor was assessed locally, or at a Novartis designated central reference laboratory if local BRAF V600 testing was unavailable. Approximately 40 patients will be enrolled to receive dabrafenib and trametinib.

The primary objective is to evaluate the antitumor activity of dabrafenib in combination with trametinib, as measured by ORR to study treatment by independent central review assessment using RANO criteria in the Full Analysis Set (FAS) population. ORR as assessed through investigator review, DOR, TTR, PFS, CBR assessed by investigator and independent central review, OS, palatability, PK, and the safety and tolerability profile of dabrafenib and trametinib are secondary endpoints.

Patients may continue to receive the assigned study treatment until disease progression by RANO criteria or loss of clinical benefit as determined by the investigator, unacceptable toxicity, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient/legal guardian, lost to follow-up, death, or study is terminated by the sponsor.

Patients who have disease progression by RANO criteria may continue study treatment if the investigator determines that patient has clear evidence of clinical benefit from study treatment, continuing study treatment may be in the best interest for the patient, and the patient/legal guardian is willing to continue on study treatment and sign the Informed Consent for treatment beyond progression. The decision to continue study treatment after PD must be documented in the patient records and eCRF after every tumor evaluation. In this case, the patient will continue assessments as defined in the study protocol section 7. An End of Treatment visit will be performed when patients permanently discontinue study treatment.

Patients who discontinue the study treatment without disease progression by RANO criteria will continue tumor assessments as outlined in the study protocol section 7 until documented

centrally confirmed disease progression by RANO criteria or death irrespective of start of new anti-neoplastic therapy.

Patients who discontinue study treatment and efficacy follow-up will enter a follow-up period during which survival will be collected every 3 months. During the survival follow-up, subsequent anti-neoplastic therapies initiated after study treatment discontinuation will be collected.

All patients will be followed for survival for at least 2 years after the last patient first study treatment (except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation).

An interim analysis (IA) for futility will be implemented to allow possible termination of recruitment and the study in the event that there is insufficient efficacy. The patients for inclusion in the formal interim analysis for futility will be determined shortly after the 16th patient is enrolled in the FAS and the analysis will be conducted when this initial group of patients to be included in the analysis have at least 20 weeks of follow-up or have withdrawn early. If the observed ORR assessed by central independent reviewer is $\leq 25\%$, there will be a consideration to stop the study due to insufficient efficacy. The final decision on whether to stop the study will take into account other available study information at the IA cut-off including safety data and all efficacy endpoints.

In addition, an interim analysis of key safety and PK data of the adolescent patients in the HGG cohort may be performed to support a health authority request for data in adolescent patients which will be a part of a separate SAP. There is no intent to declare efficacy or futility based on this interim analysis.

The primary analysis will be conducted based on the FAS when all patients have either completed at least 32 weeks of treatment (i.e. at least 24 weeks follow-up after the first post baseline tumor assessment) or have discontinued earlier. To evaluate response against the efficacy seen in existing Standard of Care (SOC) but also to provide evidence that trametinib contributes to the effect of the combination therapy, the point estimate and exact binomial confidence intervals (CIs) of ORR will be provided. The lower bound of the CIs will be used to provide evidence that the true ORR is greater than a certain specific response rate.

Final analysis will be performed when all patients have been followed for survival at least 2 years from last patient first visit, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

An independent Data Monitoring Committee (DMC) will monitor safety data approximately every 6 months from the start of study enrollment during the conduct of the study.

1.2 Study objectives and endpoints

Objective	Endpoint
Primary	
To evaluate the anti-tumor activity of dabrafenib in combination with trametinib, as measured by overall response rate (ORR) by central independent assessment using the RANO criteria.	ORR, proportion of patients with a best overall confirmed Complete Response (CR) or Partial Response (PR) by independent review assessment per Response Assessment in Neuro-Oncology (RANO) criteria.
Secondary	
a) Evaluate ORR by investigator assessment b) Evaluate duration of response (DOR) by investigator and central independent review c) Evaluate progression free survival (PFS) by investigator and central independent review d) Evaluate time to response (TTR) by investigator and central independent review e) Evaluate clinical benefit rate (CBR) by investigator and central independent review f) Evaluate overall survival (OS) g) Evaluate the safety and tolerability profile of dabrafenib in combination with trametinib in children and adolescents h) Evaluate the palatability of dabrafenib oral suspension and trametinib oral solution i) Characterize the pharmacokinetics of dabrafenib, its metabolites and trametinib in the study population	1. ORR by investigator assessment per RANO criteria 2. DOR, calculated as the time from the date of the first documented confirmed response (CR or PR) to the first documented progression or death due to any cause, as assessed separately by investigator and central independent reviewer per RANO criteria. 3. PFS, defined as time from first dose of study treatment to progression or death due to any cause, as assessed separately by central independent reviewer and investigator per RANO criteria 4. TTR, calculated as the time from the start date of study treatment to first documented confirmed response CR or PR (which must be confirmed subsequently) as assessed separately by investigator and independent central reviewer per RANO criteria 5. CBR is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of at least 24 weeks, as assessed separately by investigator and central independent reviewer per RANO criteria. 6. OS, defined as the time from first dose of study treatment to death due to any cause 7. Incidence of adverse events and serious adverse events, changes in laboratory results, vital signs, ECG and ECHO 8. Palatability questionnaire data 9. Plasma concentration-time profiles of dabrafenib, its metabolites and trametinib and PK parameters

[redacted]

Objective	Endpoint
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The interim, primary and final analyses will be performed by Novartis. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

A unique cut-off date will be determined for all analyses specified in the study protocol. The analysis cut-off date for the primary analysis of study data will be established after all enrolled patients have completed at least 32 weeks of treatment or have discontinued study earlier. For interim analysis, the patients for inclusion in the formal interim analysis for futility will be determined shortly after the 16th patient is enrolled, and the cut-off of analysis will be established when this initial group of patients to be included in the analysis have at least 20 weeks of follow-up or have withdrawn early. For final analysis, the analysis cut-off date will be established at the end of the study when all patients have been followed-up for survival at least 2 years from last patient first treatment, except if consent is withdrawn, death, or patient is lost to follow-up or study discontinuation.

For each of the analyses, all statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication records.

General analysis conventions

Pooling of centers: unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by frequency counts and percentages; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum).

2.1.1 General definitions

Investigational drug and study treatment

Study treatment will refer to dabrafenib and trametinib combination. ***Study drug*** will refer to each component of study treatment.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the Dosage Administration (e)CRF. (Example: if 1^{st} dose of dabrafenib is administered on 05-Jan-2015, and 1^{st} dose of trametinib is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015). For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per Dose Administration (e)CRF (Example: if the last dabrafenib dose is administered on 15-Apr-2014, and the last dose of trametinib is administered on 17-Apr-2014, then the date of last administration of study treatment is on 17-Apr-2014).

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, PK, performance status etc.) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment. In the rare case that time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For safety reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Notes: if data on clock time is available in the clinical database (e.g. for time of blood/urine sample taken, ECG performed, etc. and first study treatment administration), a more precise distinction between pre-treatment and on-treatment periods is encouraged to be used. If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize Karnofsky/Lansky performance status, PK, physical exam, vital signs, ECG, laboratory [redacted] data collected over time (including unscheduled visits), the assessments will be time slotted. Time windows will be defined for descriptive summary by visit. The following general rule will be applied in creating the assessment windows: if more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the worst case will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows for Karnofsky/Lansky performance status/Urinalysis

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1*	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
End of treatment		
End of treatment	N.A.	Data collected under EOT visit, if no data were collected at the EOT visit last available data obtained before EOT
Post treatment[a]		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14
Study Day 1 = start date of study treatment Post treatment study day 1=end of treatment date + 1 day ^30 days is considered to be the time until total drug elimination		

Table 2-2 Time windows for physical exam/vital signs/hematology/chemistry

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1*	≤ Study Day 1
Week 2 Day 1	Study Day 8	Study Days 6 – 10
Week 3 Day 1	Study Day 15	Study Days 13 – 17
Week 4 Day 1	Study Day 22	Study Days 20 – 24
Week 5 Day 1	Study Day 29	Study Days 27 – 31
Week 8 Day 1	Study Day 50	Study Days 43 – 57
Every 8 weeks thereafter		
Week y=8+8*k (with k = 1, 2, …, 6)	Study Day (8+8*k-1)*7+1	Study Day (8+8*k-1)*7+1-7 to (8+8*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
Every 16 weeks thereafter		
Week y=56+16*k (with k = 1, 2, …)	Study Day (56+16*k-1)*7+1	Study Day (56+16*k-1)*7+1-7 to (56+16*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
End of treatment		
End of treatment	N.A.	Data collected under EOT visit, if no data were collected at the EOT visit last available data obtained before EOT
Post treatment		
Post treatment follow-up 1	Post treatment study day 16*7	Post treatment Study Days 16*7 - 14 to 16*7 + 14
Post treatment follow-up k (with k = 2, 3, …)	Post treatment study day 16*k*7 30	Post treatment study days 16*k*7 - 14 to 16*k*7 + 14
Study Day 1 = start date of study treatment Post treatment study day 1=end of treatment date + 1 day ^30 days is considered to be the time until total drug elimination		

Table 2-3 Time windows for ECG/Visual Acuity

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (Week 1 Day 1)	On or before Study Day 1*	≤ Study Day 1
Week 5 Day 1	Study Day 29	Study Days 27 – 31

Time Window	Planned Visit Timing	Time Window Definition
Week 16 Day 1	Study Day 106	Study Days 99 – 113
Week 32 Day 1	Study Day 218	Study Days 211 – 225
Week 48 Day 1	Study Day 330	Study Days 323 – 337
Week 72 Day 1	Study Day 498	Study Days 491 – 505
Every 16 weeks thereafter		
Week y=16+16*k (with k = 1, 2, …)	Study Day (16+16*k-1)*7+1	Study Day (16+16*k-1)*7+1-7 to (16+16*k-1)*7+1+7 Note: EOT data visit are included if obtained within 30^ days of last non-0 dose intake.
End of treatment		
End of treatment	N.A.	Data collected under EOT visit, if no data were collected at the EOT visit last available data obtained before EOT
Study Day 1 = start date of study treatment Post treatment study day 1=end of treatment date + 1 day ^30 days is considered to be the time until total drug elimination		

Time windows for PK are provided in Section 7.2.3.1 of the study protocol.

For all analyses regarding abnormal assessments or analyses based on worst or best post-baseline value (laboratory, ECGs, vital signs, Karnofsky/Lansky performance status, ECHO, ophthalmologic exam, dermatologic exam, etc.), all post-baseline values will be included (scheduled, unscheduled, repeat).

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-4 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.

Source data	Conditions
Tumor (RANO) assessment date	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will NOT be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF. If the day is missing from the date of last contact, it will be imputed to the 15th day of the month and year of last contact only if derived from the survival page.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The **Full Analysis Set** (FAS) comprises all patients to whom study treatment has been assigned and who received at least one dose of study treatment.

Safety Set

The **Safety Set** includes all patients who received at least one dose of any component of the study treatment.

Evaluable Set

The **Evaluable Set** consists of all evaluable patients in the FAS who have centrally confirmed HGG through histology, centrally confirmed positive BRAF V600 mutation, an adequate tumor assessment at baseline, a follow-up tumor assessment at least 8 weeks after starting treatment (unless disease progression is observed before that time) or have discontinued for any reason. An adequate tumor assessment at baseline refers to baseline measurable disease assessed by investigator and confirmed by central independent reviewer per RANO criteria.

The evaluable set will be used for sensitivity analyses as defined in sections 2.5 and 2.7.

Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) consists of all patients who receive at least one (full or partial) dose of dabrafenib or trametinib and provide at least one evaluable pharmacokinetic (PK) blood sample.

A sample is considered evaluable if all of the following conditions are satisfied:

- Patient did not vomit within 4 hours after the dosing of dabrafenib/trametinib prior to sampling;
- For pre-dose samples: have the sample collected before the next dose administration.

Validity of PK samples will be confirmed by checking sampling time window and occurrence of vomiting with respect to time of dose when PK profile is sampled. Only confirmed PK concentrations will be used in the analyses.

Additionally, a sample can be considered to be not evaluable as per scientific judgment of the clinical pharmacology expert. When a sample is considered not evaluable by the clinical pharmacology expert, the reason will be documented.

The PAS will be used in the analysis of PK data. Any blood samples missing blood collection date or time, or missing associated study drug dosing date or time will be excluded.

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific patient classification rules defined in Table 2-5 Patient classification based on protocol deviations and non-PD criteria

Table 2-5 Patient classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	No dose of study medication
Safety Set	No written inform consent	No dose of study medication
Evaluable Set		Not centrally confirmed measurable disease at baseline, Not centrally confirmed HGG, Not centrally confirmed BRAF V600 mutant, Patients who do not have an adequate tumor assessment at baseline, and a follow-up tumor assessment at least 8 weeks (±1 week visit window) after starting treatment unless disease

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
		progression is observed before that time.
PK Analysis Set	Relevant PD criterion	Patients who do not have at least one evaluable PK sample as defined above

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis data sets. The date on which a patient withdraws full consent is recorded in the eCRF.

Death events may be used in the analysis if captured from public records (registers), local law and subject informed consent permitting.

Additional data for which there is a separate informed consent, e.g. PK, [redacted] etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroups of interest

Efficacy

The primary efficacy endpoint ORR and secondary endpoint DOR by investigator and central independent review assessments may be summarized by risk categories such as that determined by methylation analysis based on FAS and Evaluable set. The risk categories will be specified in a later SAP amendment prior to final database lock [redacted].

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and confidence intervals will be provided. The objective of the efficacy subgroup analysis is to assess homogeneity of treatment effect in the above subgroups. In addition, efficacy data for patients enrolled in Japan will also be reported separately.

Safety

Safety subgroup analyses will use the same method as for the analysis in the safety analysis set. Key safety analyses including:

- Overview of AEs
- AEs, regardless of relationship to study drug, by primary system organ class and preferred term
- AEs related to the study drug, by primary system organ class and preferred term

- Serious AEs, regardless of relationship to study drug, by primary system organ class and preferred term

will be repeated on safety set in the following subgroups:

- Age group (12 months- <6 years, 6 -< 12 years, 12 -< 18 years)
- Any prior antineoplastic chemotherapy (yes, no)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients.

Exposure data will be presented by the following subgroups:

- Dabrafenib: Age group (< 12 years, ≥ 12 years)
- Trametinib: Age group (< 6 years, ≥ 6 years)

For data that require a summary table by subgroup, a listing may be sufficient if less than 10% of patients or less than 10 patients are present in each subgroup.

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, age groups: 12 months-<6 years, 6 -< 12 years, and 12 -< 18 years, race, ethnicity, height, weight, BMI, Karnofsky/Lansky performance status, [redacted]) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body surface area (BSA)) will be summarized by descriptive statistics (n, mean, median, standard deviation, 25th and 75th percentiles, minimum and maximum). BSA will be calculated using Gehan and George formula: BSA[m2] = 234.94 * (height[cm] ** 0.422) * (weight[kg] ** 0.515) /10000 unless otherwise specified.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, pathology at initial diagnosis, histological grade for initial diagnosis, time since initial diagnosis, time from initial diagnosis to first recurrence/progression (in months), presence/absence of target and non-target lesions and BRAF mutation status (local or central result used to determine eligibility, as applicable). Note: Presence/absence of target and non-target lesions will be based on the data collected on RANO target/non-target lesion assessment eCRF pages.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF pages will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline, including source of patient referral, child bearing potential, [redacted] will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also using the FAS. The number (%) of treated patients included in the FAS will be presented. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided: % based on the total number of FAS patients:

- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered);
- Number (%) of patients who are still on-treatment and do not have RANO-defined progression of disease assessed by investigator (based on the 'End of Treatment Disposition' page not completed and no PD reported on the RANO pages);
- Number (%) of patients who are still on-treatment post RANO-defined progression of disease assessed by investigator (based on the 'Confirmation of Favorable Clinical Benefit from Study Treatment' page, the 'End of Treatment Disposition' not completed , and PD reported on the RANO pages);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Disposition' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post Treatment Phase Disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post Treatment Phase Disposition' page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Disposition' or 'End of Post Treatment Phase Disposition' page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan). Protocol deviations leading to exclusion from analysis sets will be listed. [redacted]

Analysis sets

The number and percentages (based on the total number of FAS patients) of patients in each analysis set (defined in Section 2.2) will be summarized.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized separately for dabrafenib and trametinib. The duration of exposure will also be presented for the study treatment of dabrafenib and trametinib combination therapy. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by dabrafenib and trametinib.

Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

The Safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to any combination partner.

Duration of exposure to study treatment (day*s*) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the latest of the last dates of exposure to any combination partner (see Table 2-6 Definition of last date of exposure of study drug).

Summary of duration of exposure of study treatment in appropriate time units based on clinically meaningful time intervals (eg 8-<24, 24-<56, 56-<112, >= 112 (weeks)) will include categorical summaries and continuous summaries (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum) using appropriate units of time.

Duration of exposure to combination partner

Duration of exposure to a study drug (days) = (last date of exposure to investigational drug) – (date of first administration of investigational drug) + 1.

Table 2-6 Definition of last date of exposure of study drug

Definition of last date of exposure of study drug	Example
Date of last administration of a non -zero dose of the study drug.	A patient had a permanent discontinuation of the study drug 06Jan2013 after being put on a temporary interruption since 01Jan2013. In this case the last date of exposure is 31Dec2012.

Summary of duration of exposure to each combination partner will include categorical summaries based on clinically meaningful time intervals (8-<24, 24-<56, 56-<112, >= 112 (weeks)) and using descriptive statistics (i.e. n, mean, standard deviation, median, 25^{th}-75^{th} percentiles, minimum, and maximum) using appropriate units of time.

Cumulative dose and average daily dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study drug, respectively. Average daily dose is defined as [Cumulative dose (dosing unit) / Number of dosing days]; drug free days are not counted as dosing days.

Cumulative dose and average daily dose will be summarized both in mg and mg/kg. Total actual cumulative dose (mg/kg) of dabrafenib and trametinib is calculated as the sum of the daily doses in mg/kg, where the mg/kg dose on any particular day is calculated as the dose in mg divided by the current weight (collected as per the visit schedule). Total actual cumulative dose (mg) of dabrafenib and trametinib is calculated as the sum of the daily doses in mg.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of study drug administration. The planned dose (mg) will be taken from the planned dose (mg) times the frequency from the first dosing record. The planned cumulative dose will not be summarized/listed. It will be used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered over the duration for which the patient is on the study treatment as documented in the Dose Administration eCRF page.

For patients who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

Dose intensity and relative dose intensity

Dose of dabrafenib and trametinib will be defined in the units of mg, and taken from the dose administration CRF.

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg/ day) = Actual Cumulative dose (mg) / Duration of exposure (day).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (mg/ day) = Planned Cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/ day) / PDI (mg/ day).

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components.

Summary of RDI will include categorical summaries based on clinically meaningful intervals (<50%, 50-<75%, 75-<90%, 90-<110%, >=110%.)

Table 2-7 Examples of dabrafenib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg) frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption ?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 05Jan2016	125 mg BID	250	No	No	
2	06Jan2016 / 03Feb2016	125 mg BID	200	Yes	No	AE
3	04Feb2016 / 25Feb2016	130 mg BID	260	Yes	No	As per protocol

Duration of exposure (days) = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 125*2*56 days = 14000 mg

Actual cumulative dose = 250*5 + 200*29 + 260*22 = 12770 mg

Dose intensity = 12770 mg / 56 days = 228.04 mg/day

Planned dose intensity = 14000 mg / 56 days = 250 mg/day

Relative dose intensity = DI / PDI = (228.04 mg/day) / (250 mg/day) = 91.2%

Table 2-8 Examples of trametinib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
1	01Jan2016 / 10Jan2016	0.875 QD	0.875	No	No	
2	11Jan2016 / 15Jan2016	0.875 QD	0	Yes	No	AE

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption?	Dose Permanently Discontinued	Reason
3	16Jan2016 / 25Feb2016	0.75 QD	0.75	No	No	AE

Duration of exposure = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 0.875*56 days = 49 mg

Actual cumulative dose = 0.875*10 + 0*5 + 0.75*41 = 39.5 mg

Dose intensity = 39.5 mg / 56 days = 0.705 mg/day

Planned dose intensity = 49 mg / 56 days = 0.875 mg/day

Relative dose intensity = DI / PDI = (0.705 mg/day) / (0.875 mg/day) = 80.6%

Dose reductions, interruptions or permanent discontinuations

The number of patients who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study drug.

'Dose interrupted' and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions and permanent discontinuations, respectively. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this block of entries, then it will be counted as one interruption.

Dose Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

Missing data: If dose is recorded but regimen is missing or entered as 'none', it is assumed that the investigational drug was taken as per-protocol.

2.4.2 Prior, concomitant, on study and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy etc.), setting (e.g. adjuvant, metastatic, etc.) and also by lowest ATC class and preferred term. Summaries will include total number of regimens, best response and time from last treatment to progression for the last therapy. The medication therapy type of any combination therapy will be classified based on the following order: chemotherapy, biologic therapy, targeted therapy, hormonal therapy. For example, a combination therapy of chemotherapy and hormonal therapy will be classified as 'chemotherapy'. For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

On-study Radiotherapy and Surgery

As on study radiotherapy is allowed after centrally confirmed radiologic progression of disease or at least a total of 36 months of treatment plus follow-up, whichever comes first, surgeries and radiotherapies occurring on study will be listed only.

For patients enrolled in the HGG cohort, anti-cancer surgery is allowed for patients enrolled on the study after at least 8 months on treatment or after radiologic progression of disease has been confirmed by investigator. Study treatment may be taken up to one day prior to surgery as deemed appropriate by the investigator.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, and by means of frequency counts and percentages using FAS. In addition, listings will include best response to the regimen.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Non-drug therapies and procedures starting after the start of study treatment will also be summarized by SOC and preferred term.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Concomitant medications that have the potential to impact some specific analyses (e.g. PK, efficacy or safety analyses) will be identified prior to database lock. Separate summaries of these concomitant medications will be produced using the appropriate analysis set (e.g. FAS for those potentially affecting efficacy. According to the study protocol, treatment with substances which are strong inhibitors, or inducers of CYP3A4/5 and CYP2C8, or antiretrovirals or herbal medicines or other anti-cancer or anti-investigational drugs should be avoided. However, some patients may take these substances during the treatment period so these concomitant medications will be selected via programming and tabulated and listed in the Clinical Study Report. Treatment with the prohibited substances mentioned above will be identified in the database as protocol deviations.

2.5 Analysis of the primary objective

The primary objective is to demonstrate the antitumor activity of dabrafenib in combination with trametinib as measured by overall response rate (ORR) to study treatment by central independent review assessment using RANO criteria, in children and adolescent patients with BRAF V600 mutation positive relapsed or refractory High Grade Glioma (HGG).

2.5.1 Primary endpoint

ORR is defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) according to RANO criteria (see Appendix 3 of the study protocol). ORR will be calculated based on the FAS using central independent review of tumor assessment data. Only tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR. See Appendix 5.5 for primary estimand definition.

Best overall response

The BOR will be assessed based on reported responses across all evaluation time points. Both CR and PR must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met. The next scheduled assessment may be used for purposes of confirmation of response. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

BOR for each patient is determined from the sequence of overall responses according to the following rules, up to progression:

- CR = at least two determinations of CR at least 4 weeks apart before progression
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
- SD = requires at least one SD assessment (or better) determined at or beyond the second regularly scheduled tumor assessment (nominally week 16 i.e >= 105 days allowing for the ±1 week visit window) after start of study treatment (and not qualifying for CR or PR).
- PD = progression after start of study treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD at or beyond the second regularly scheduled post-baseline tumor assessment or progression)

If a patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the BOR determination. Further anti-neoplastic therapies will be identified via protocol deviations or from the data collected on 'Anti-neoplastic therapies since last date of study drug' as appropriate.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed on the FAS. Point estimate and exact confidence intervals (CIs) [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413] of ORR will be provided. The lower bound of the CIs will be used to provide evidence that the true ORR is greater than a certain specific response rate.

The 95% CI, via the lower limit, is used to establish the levels of response which are exceeded by taking the combination therapy according to a robust standard of evidence (i.e. one-sided alpha=0.025). For example, out of 40 patients who have been enrolled and have completed at least 32 weeks of treatment or have discontinued treatment earlier, if 14 responses (35%) are observed then the corresponding 95% CI will exclude 20% which is greater, than the typical standard of care response rate previously observed [Lashford LS, Thiesse P, Jouvet A, et al. (2002); Nicholson HS, Kretschmar CS, Krailo M, et al. (2007) ; Ruggiero A, Cefalo G, Garre ML, et al. (2006) ; Warren KE, Gururangan S, Geyer JR, et al. (2012) ; Hummel TR., Wagner L, Ahern C., et al. (2013)].

The study also aims to provide evidence that trametinib gives added value to the dabrafenib plus trametinib combination over and above dabrafenib monotherapy treatment. Since a lower standard of evidence is usually required to show such added value the lower limit of an 80% CI

is used to identify the response rates which will be exceeded by taking the combination therapy based on a reduced level of evidence (one-sided alpha of 0.1). For example, if 18 responses (45%) out of the 40 patients are observed then the lower bound of 80% CI will exclude 32%, which is the response rate of dabrafenib monotherapy observed from the study DRB436A2102. In addition, the 95% CI can also be used to provide more robust evidence of the added benefit of trametinib. For example, if 20 responses (50%) are observed, then the lower bound of 95% CI will also exclude 32%.

2.5.3 Handling of missing values/censoring/discontinuations

Patients with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'failures'.

2.5.4 Supportive analyses

As sensitivity analysis, ORR will be calculated and summarized for patients from the Evaluable Set. ORR will be summarized using descriptive statistics (N, %) along with two-sided exact binomial 95% and 80% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

New anticancer therapy sensitivity analysis for ORR

The analyses of ORR will be repeated using a stricter ITT approach i.e including all response assessments irrespective of new anti-neoplastic therapy using the FAS. This analysis will only be performed if data permits.

Response evaluations recorded after the initiation of new anti-neoplastic therapy will be included in sensitivity analysis of ORR, (i.e. the occurrence of new anti-neoplastic therapy will be ignored for the analyses). The sensitivity analyses will be performed based on both the investigator and independent review assessments using the FAS. In the summary tables, this approach is referred as 'new anticancer therapy ORR sensitivity analysis'.

Concordance analysis of ORR

An assessment of the concordance between central independent reviewer assessment and local investigator assessment of the Best Overall Response for each patient will be provided. The calculation will be based on the percent agreement (the proportion of response outcomes that agree or match across both Independent Reviewer and Investigator Assessments).

Reasons for "Unknown" BOR

Patients with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response UNK
- New anti-neoplastic therapy started before first post-baseline assessment

- SD and/or unconfirmed CR/PR only occurring prior to week 16 visit

2.6 Analysis of the key secondary objective

Not Applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are to:

- Evaluate ORR by investigator assessment per RANO
- Evaluate duration of response (DOR) by investigator and central independent review per RANO
- Evaluate progression-free (PFS) survival by investigators and central independent review assessment per RANO
- Evaluate time to response (TTR) by investigators and central independent review assessment per RANO
- Evaluate CBR by investigators and central independent review assessment per RANO
- Evaluate overall survival (OS)

2.7.1 Secondary endpoints

ORR by investigator assessment

The evaluation of ORR will be repeated by investigator assessment as per RANO criteria based on the FAS and the Evaluable Set separately. ORR will be summarized using descriptive statistics (N, %) along with 2-sided exact 95% and 80% confidence intervals (CIs) [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

Duration of response

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to RANO criteria. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression per RANO or death due to any cause. If a patient has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, DOR will be censored at the date of the last adequate tumor evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier (see Section 2.7.3).

DOR will be analyzed as per investigator and central independent reviewer assessments separately. The analyses of DOR will be based on the FAS and will be repeated based on the Evaluable set.

Progression free survival

Progression free survival (PFS) is defined as the time from the start date of study treatment to the date of the first documented progression or death due to any cause. PFS will be calculated

using RANO criteria based on investigators and central independent review of tumor assessments separately. The analysis will include all data observed up-to the cut-off date. If a patient has not progressed or died or has received any further anticancer therapy at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier. (See Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment). Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages) without supporting evidence satisfying progression criteria per RANO will not be considered disease progression for PFS derivation. The analysis will be based on FAS and Evaluable Set separately.

Time to response

Time to response (CR or PR) is the time from start date of study treatment to first documented response of CR or PR (which must be confirmed subsequently) according to RANO criteria. All patients in the FAS will be included in the time to response calculation. Patients who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FPFV - LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other patients.

TTR will be analyzed using investigator and independent reviewer assessments separately.

Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD which lasts for a minimum time duration of 24 weeks. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 23 weeks or later (i.e >= 161 days) from treatment start date, allowing for the ±1 week visit window for tumor assessments.

CBR will be analyzed using investigator and independent reviewer assessments separately. CBR will be calculated using the FAS set and Evaluable Set separately.

Overall Survival

Overall Survival (OS) is defined as the time from start date of study treatment to date of death due to any cause. A cut-off date will be established for each analysis of OS. All deaths occurring on or before the cut-off date in the FAS will be used in the OS analysis.

If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact (Section 2.1.1) .

2.7.2 Statistical hypothesis, model, and method of analysis

ORR by investigator assessment

ORR assessed by investigator assessment per RANO criteria will be summarized using descriptive statistics (n, %) along with two-sided exact binomial 95% CIs and 80% CIs [Clopper

CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

All response data will be listed by investigator and central independent review assessment.

Time to response

Time to response data will be listed and summarized. The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. In addition, a responders-only analysis will also be performed in this case using descriptive summary statistics.

Duration of response

DOR will be listed and summarized for all patients with confirmed BOR of CR or PR. If a sufficient number of response is observed, the Kaplan-Meier estimate of the distribution function will be constructed. The number of patients at risk at certain time points will be shown on the plot. The estimated median (in weeks) along with 95% CIs, as well as 25th and 75th percentiles will be reported. [Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-22.

Brookmeyer R and Crowley J. (1982)]. In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs [Kalbfleisch JD and Prentice RL. (2002)] at several time points (including at least 4, 6, and 12 months) will be summarized. Censoring reasons will also be summarized.

Progression Free Survival

PFS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at 6, 12, 18 and 24 months. Censoring reasons will also be summarized.

Clinical Benefit Rate

CBR will be summarized using descriptive statistics (n, %) along with two-sided exact binomial 95% CIs [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

Overall Survival

OS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR, including estimated median (in months) with 95% CI [Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-22.

Brookmeyer R and Crowley J. (1982)], 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at timepoints including 6, 12, 18 and 24 months.

2.7.3 Handling of missing values/censoring/discontinuations

DOR and PFS

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy, DOR and PFS will be censored at the date of the last adequate tumor before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the start date of treatment will be used.

In particular, DOR and PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is administered; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-9 for censoring and event date options and outcomes for DOR and PFS.

Table 2-9 Outcome and event/censor dates for DOR and PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of start of study treatment	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim*	Date of last adequate assessment	Censored
New anticancer therapy (including cancer related surgery and radiotherapy) given prior to protocol defined progression	Date of last adequate assessment on or prior to starting new anti-cancer therapy	Censored

Situation	Date	Outcome
Death before first PD assessment	Date of death	PFS event

* This refers to undocumented progression based on investigator claim only. Clinical Status will be considered as appropriate in the determination of progression per RANO criteria.

Censoring pattern of PFS

Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Initiation of new cancer therapy prior to progression
6: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments (see Section 2.7.3 for definition):

1. Analysis cut-off date,
2. Start date of further anti-neoplastic therapy,
3. Date of consent withdrawal,
4. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. ‘Ongoing’,
2. ‘New cancer therapy added’,
3. ‘Withdrew consent’,
4. ‘Lost to follow-up’,

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed. then the PFS censoring reason will always default to ‘Adequate assessment no longer available’. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than the interval of 2 missing tumor assessments then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced for PFS by investigator and central independent reviewers. The censoring patterns will be compared between investigator and central independent reviewers.

OS

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date patient was alive, i.e., last contact date (see Section 2.1.1).

2.7.4 Supportive analyses

ORR, DOR, and PFS based on radiographic response by independent review assessment

The analyses of ORR, DOR, and PFS will be repeated based on radiographic response assessed by independent review by only incorporating the radiographic data which includes the lesion measurements from target lesions, non-target lesions, and new lesion per RANO. Clinical status data and corticosteroid use data will not be considered for the supportive analyses based on radiographic response. Waterfall plot will be presented for this analysis.

Waterfall graphs will be used to depict the anti-tumor activity for independent and investigator assessments.. These plots will display the best percentage change from baseline in the sum of the products of perpendicular diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall graphs. Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. A patient with only such assessments will be represented by a special symbol (e.g. ✶) in the waterfall graph. Assessments with "unknown" target lesion response and assessments with unknown overall response will be denoted in the waterfall plots. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of patients with tumor shrinkage and tumor growth. Bars will have different fill patterns for all possible values of overall response. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-10.

Table 2-10 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
case	Target response	Overall lesion response	Include in waterfall?	Non-target response	New lesion?
1	CR/PR/SD	PD	Yes as a bar	PD	any
2	CR/PR/SD	PD	Yes as a bar	any	Yes
3	UNK	UNK or PD	Yes as an x	any	any
4	CR/PR/SD	UNK	Yes as a bar	UNK	No
5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
6	PD	PD	Yes as a bar	any	any

Additionally, swimmer plots of time to onset and duration of response based on independent and investigator review will be created for the FAS.

Corticosteroids use

The drug name, dose, reason, dosing frequency per interval, and dose intensity will be listed. The dose intensity is calculated as the cumulative dose divided by the duration of exposure per interval. Any corticosteroids use starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

New anticancer therapy sensitivity analysis for DOR and PFS

Response evaluations and events (i.e. RANO. documented disease progression or death) recorded after the initiation of new anti-neoplastic therapy will be included in sensitivity analyses of DOR and PFS, (i.e. the occurrence of new anti-neoplastic therapy will be ignored for the analyses). The sensitivity analyses will be performed based on both the investigator and independent review assessments using the FAS and using the same statistical methods for DOR and PFS described in Section 2.7.2. In the summary tables, this approach is referred as 'new anticancer therapy DOR sensitivity analysis' and 'new anticancer therapy PFS sensitivity analysis'.

2.8 Safety analyses

All safety analyses will be based on the safety set unless otherwise specified.

2.8.1 Adverse events (AEs)

Adverse events are coded using MedDRA terminology. The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class (SOC) will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

The following AE summaries will be produced: overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE, any dose reductions/interruptions etc.), AEs by SOC and PT, summarized by relationship to study treatment (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, and leading to fatal outcome. In addition, a summary of serious and non-serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term) as per EudraCT requirements.

For legal requirements of clinicaltrials.gov and EudraCT, two required tables for on-treatment adverse events which are not SAE's with an incidence greater than and equal to 5% and on-treatment SAE's and SAE's suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population

2.8.1.1 Adverse events of special interest / grouping of AEs

All AE groupings for a clinical program are stored in the Compound Case Retrieval Strategy sheet (CRS) with clear versioning and reference to the MedDRA version used.

All AESI definitions or AE grouping need to be specified in the CRS. If a CRS update is necessary, the final version needs to be available in a reasonable time ahead of the DBL. The CRS version should be included in a footnote of the AESI tables.

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to dabrafenib and trametinib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

AESI for dabrafenib and trametinib are:

- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Hypertension

- Pyrexia
- Pre-Renal and intrinsic renal failure
- Uveitis
- New primary /secondary malignancy
- Hypersensitivity
- Hyperglycemia
- Venous thromboembolism
- Pancreatitis
- Neutropenia

Summaries of these AESIs will be provided by dabrafenib and trametinib, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, fatal outcome, etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths including on-treatment and post-treatment deaths will be produced by system organ class and preferred term.

All deaths will be listed for the Safety set, post-treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.8.3 Laboratory data

Data handling

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Data analysis

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of lab parameter values for serum creatinine over time (baseline and selected on-treatment time points) will be displayed via boxplots based on time windows for patients with values at baseline and 6 months or greater and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBIL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

Potential Hy's Law events are defined as those patients with occurrence of AST or ALT > 3xULN and TBL > 2xULN and missing ALP or ALP < 2xULN at any time during the on-treatment period . Note that the criteria relating to combined elevations of AST (or ALT) and TBL are based on the peak values at any post-baseline time for a subject.

For patients with abnormal ALT or AST baseline values, a clinically significant liver safety signal corresponding to Hy's law is defined by : [ALT or AST > 3xbaseline] OR [ALT or AST >8xULN], whichever is lower, combined with [TBIL >2xbaseline AND >2*ULN]A figure displaying time course of hepatic function tests (ALT, AST, TBL, ALP) in patients meeting Hy's criteria will be displayed in the Safety Set. Additonally, evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be produced to display ALT and AST values by TBL values in units of ULN.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

ECG Data analysis

Standard 12-lead ECGs including PR, QRS, QT, QTcF, and HR intervals will be obtained local for each patient during the study. ECG data will be read and interpreted locally.

The number and percentage of patients with notable ECG values will be presented:

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

The normal range for HR is displayed in Table 2-11 Recommendation for normal heart rate per age group and gender. The number and percentage of patients with notable values will be presented.

Table 2-11 Recommendation for normal heart rate per age group and gender

Age group	0-1 month	1-3 months	3-6 months	6-12 months	1-3 years	3-5 years	5-8 years	8-12 years	12-18 years
HR (bpm) Boys	(125, 190)	(125, 185)	(110, 165)	(105, 165)	(95, 155)	(75, 125)	(60, 115)	(55, 100)	(50, 100)
HR (bpm) Girls	(135, 215)	(125, 200)	(120, 190)	(105, 185)	(95, 180)	(80, 125)	(70, 115)	(60, 110)	(50, 100)

Data shown as upper limit of normal, lower limit of normal for HR= heart rate. Ref.: adapted from Rijnbeek et al. 2001.

The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. A listing of all ECG assessments will be produced and notable values will be flagged. A separate listing of only the patients with notable ECG values may also be produced. In the listings, the assessments collected during the post-treatment period will be flagged.

The denominator to calculate percentages for each category is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline ECG notable value is defined as a post-baseline value that meets the criterion post-baseline but did not meet the criterion at baseline.

For each ECG parameter, descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized. Descriptive statistics at worst post-baseline and changes from baseline to worst post-baseline will also be summarized separately.

For each of the QTc and QT intervals, shift tables based on notable parameter categories (<450, 450-<481, 481-<501, ≥501 ms) at baseline and the worst post-baseline value observed.

Frequency counts and percentages of patients with newly occurring post-baseline qualitative ECG abnormalities (morphology) will be summarized. The denominator to calculate percentages is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline qualitative ECG abnormality is defined as a post-baseline abnormal finding which was not present at baseline.

Patients with notable ECG interval values and newly occurring qualitative ECG abnormalities will be listed and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

ECHO Data handling

ECHO data will be analyzed based on local reported results. The summaries will include all ECHO assessments performed no later than 30 days after the last date of study drug. All ECHO

assessments will be listed, and those collected later than 30 days after study drug discontinuation will be flagged in the listing.

The same modality (ECHO or MUGA) for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) should be used to follow a patient throughout the study. The absolute change from baseline values will not be calculated for any patients where the post-baseline value was determined by a cardiac scan modality that is different than the one used to determine baseline value.

ECHO Data analysis

Absolute change from baseline in LVEF will be summarized in the worst case post-baseline. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- No change or any increase
- Any decrease:
  - > 0 - <10% Decrease
  - 10 - <20% Decrease
  - ≥20% Decrease
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

ECHO assessments of LVEF will be listed for each patient including absolute change from baseline at each assessed time interval. The values of potential clinical importance will also be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters are being collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-12 Criteria for notably abnormal vital signs below.

Table 2-12 Criteria for notably abnormal vital signs

	Clinically notable criteria			
Vital sign (unit)	High		Low	
Systolic blood pressure [mmHg]	≥ 95th percentile of the age and height group[1]		≤ 5th percentile of the age and height group[1]	
Diastolic blood pressure [mmHg]	≥ 95th percentile of the age and height group[1]		≤ 5th percentile of the age and height group[1]	
Body temperature [°C]	≥ 38.4°C		≤ 35.0°C	
Pulse rate [bpm][2]	12-18 months	> 140	12-18 months	< 103
	18-24 months	> 135	18-24 months	< 98
	2-3 years	> 128	2-3 years	< 92
	3-4 years	> 123	3-4 years	< 86
	4-6 years	> 117	4-6 years	< 81
	6-8 years	> 111	6-8 years	< 74
	8-12 years	> 103	8-12 years	< 67
	12-15 years	> 96	12-15 years	< 62
	≥ 15 years	> 92	≥ 15 years	< 58
Weight	increase from baseline[3] of ≥ 2 BMI-for-age percentile categories[4]		decrease from baseline[3] of ≥ 2 BMI-for-age percentile categories[4]	

bpm=beats per minute; CDC= Centers for Disease Controls and prevention; NHLBI= National Heart, Lung, and Blood Institute;

[1] Blood pressure percentiles are calculated for each blood BP record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

Note: Methods applies to patients less than 3 years old.

[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; 377: 1011-18.

[3] Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to or greater than the 95th percentile);

[4] BMI-for-age percentiles categories (P3, P5, P15, P25, P50, P75, P85, P95, P97) are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/);

Note: For patients less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the recumbent length; for patients over 228 months- old, percentiles are not available and will be considered as missing.

The number and percentage of patients with notable vital sign values (high/low) will be presented.

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP. Baseline is defined as the last non-missing value prior to or coinciding with first dose. The worst post-baseline value refers to the worst post-baseline value on treatment.

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure. For each parameter, only patients with a value at both baseline and post baseline (on treatment) will be included.

A listing of all vital sign assessments will be produced by and notable values will be flagged. A separate listing of only the patients with notable vital sign values may also be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Performance status

The Karnofsky and Lansky performance status scale (Table 2-13 Performance status criteria) will be used to assess physical health of patients:

Table 2-13 Performance status criteria

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be in multiples of 10			
Karnofsky (age >16 years of age)		**Lansky** (age <16 years)	
Score	**Description**	**Score**	**Description**
100	Normal, no complaints no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity, minor signs of symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort, some signs of symptoms of disease.	80	Active, but tires quickly.
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play, keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.

Frequency counts and percentages of patients in the score category of 100, 90, 80, 70, and < 70 will be provided by time point based on the windows defined in Section 2.1.1. A summary of change from baseline by scheduled visits will be performed, as well as the worst case post-baseline and the best case post-baseline changes during the study.

A supporting listing will also be provided.

2.8.4.4 Dermatological Evaluation

Skin examination results will be summarized by frequency counts and percentages of patients in each category (normal, abnormal) by scheduled time points. A supporting listing will also be provided.

[redacted]

2.8.4.7 Growth and development (Height and Weight)

Growth data consist of height, weight, BMI, height velocity and weight velocity.

Height and BMI will be summarized at 6-month intervals, using the standard deviation scores (SDS, also called z-score), velocity and velocity SDS. The relevant height and weight values for each 6-month period are defined using time windows, as defined in Table 5-3. The z-scores will allow identification of potential outliers.

The formula used to calculate the SDS and height and weight velocities are provided in the Appendix 5.3.2.

Note that BMI SDS are reported instead of weight SDS as no reference data for weight are provided by the WHO for age beyond 10.

Height and BMI SDS and heigh and weight velocity SDS will be summarized using descriptive statistics (mean, standard deviation, range) for each time window (at Baseline and thereafter allowing informal comparison of growth data), as well as by presenting number of patients with SDS values lower/higher than 5_{th}/95_{th} percentiles respectively.

Box plots will be plotted for each time window. A shift table to compare baseline SDS to the worst on-treatment SDS categorized as Low (SDS <- 1.645), High (SDS > 1.645) or Normal (-1.645 ≤ SDS ≤ 1.645) will be produced for height and BMI SDS. Another shift table to compare the baseline height SDS to the last available on-treatment height SDS categorized according to the main percentile lines (>95^{th}, 95^{th} to 90^{th}, 90^{th} to 75^{th}, 75^{th} to 50^{th}, 50^{th} to 25^{th}, 25^{th} to 10^{th}, 10^{th} to 5^{th} and ≤5^{th} percentile) will be produced. All height and BMI SDS, velocity and velocity SDS data will be listed, and values of SDS and velocity SDS outside of the central 95% of population values will be flagged as either High (SDS > 1.645) or Low (SDS < -1.645).

2.8.4.8 Ophthalmologic exam

Visual acuity will be converted from snellen to logMAR scale as defined in Holladay 1997 (20), and categorized as the following change from baseline:

- Improvement: ≥ 0.2 logMAR improvement (decrease in logMAR)
- Stable: neither ≥ 0.2 logMAR improvement nor worsening, where
- Worsening: ≥ 0.2 logMAR worsening (increase in logMAR)

Visual acuity categories at each time point, as well as best and worst category on treatment will be presented. [redacted] Data from ophthalmologic exams will be listed.

[redacted]

2.8.4.10 Palatability

Data on palatability assessments for dabrafenib and trametinib oral solutions (bitterness, sweetness, texture and overall taste) will be summarized and listed.

2.8.4.11 Additional analyses

Time to first occurrence

Time to first occurrence of an event is defined as time from start of study treatment to the date of first occurrence of this event (or first event within an AE grouping), i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.

For Kaplan-Meier analyses of time to occurrence, in the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- new anticancer antineoplastic therapy start date
- end date of on-treatment period
- data cut-off date
- withdrawal of informed consent date.

Failure curves (ascending Kaplan-Meier curves) will be constructed. Median together with 95% confidence interval as well as 25th percentile and 75th percentile will be presented.

In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

2.9 Pharmacokinetic endpoints

All PK analyses will be performed based on the PAS unless otherwise specified.

PK parameters

For subjects where dense PK collected on Day 15 the PK parameters that will be determined if data permit are shown in Table 2-14 Non-compartmental PK parameters for dabrafenib and trametinib. The PK parameters will be derived using non-compartmental methods using WinNonlin® software version 6.4.

Table 2-14 Non-compartmental PK parameters for dabrafenib and trametinib

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (ng*h/mL)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (ng*h/mL); tau= 12 hrs
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (h).

Ctrough	Measured concentration at the end of a dosing interval at steady state (taken directly before next administration) (ng/mL)The trough (predose) plasma concentration determined directly from the raw concentration-time data
Cavg	Steady state average plasma concentration (ng/mL)
Tlast	The last measurable concentration sampling time for the AUClast calculation (h)

Descriptive statistics (n, mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented for Pharmacokinetic analysis set for all dabrafenib (and its metabolites) and trametinib PK parameters defined in Table 2-14 Non-compartmental PK parameters for dabrafenib and trametinib, except Tmax and Tlast, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed using the Full analysis set.

PK concentrations

Only valid PK concentrations will be used in the analyses as defined in Section 2.2.

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for dabrafenib, metabolites and trametinib concentrations will be presented by each scheduled time point and actual leading dose (i.e. the dose taken on the day prior to the PK sampling day) for the Pharmacokinetic analysis set. Zero concentrations will not be included in the geometric mean calculation. Graphical presentation will be provided on mean concentration at each scheduled time point for PK sub-population where the full PK profile is available.

Individual concentration-time profiles for dabrafenib and trametinib concentrations with median will be displayed graphically by treatment for Full analysis set on the semi-log view. In addition, the mean (+/- SD) and geometric mean concentration-time profiles for dabrafenib (+ its metabolites) and trametinib over time will be displayed graphically for Pharmacokinetic analysis set on the linear and semi-log view.

All individual plasma dabrafenib metabolites and trametinib concentration data will be listed for the Full analysis set.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

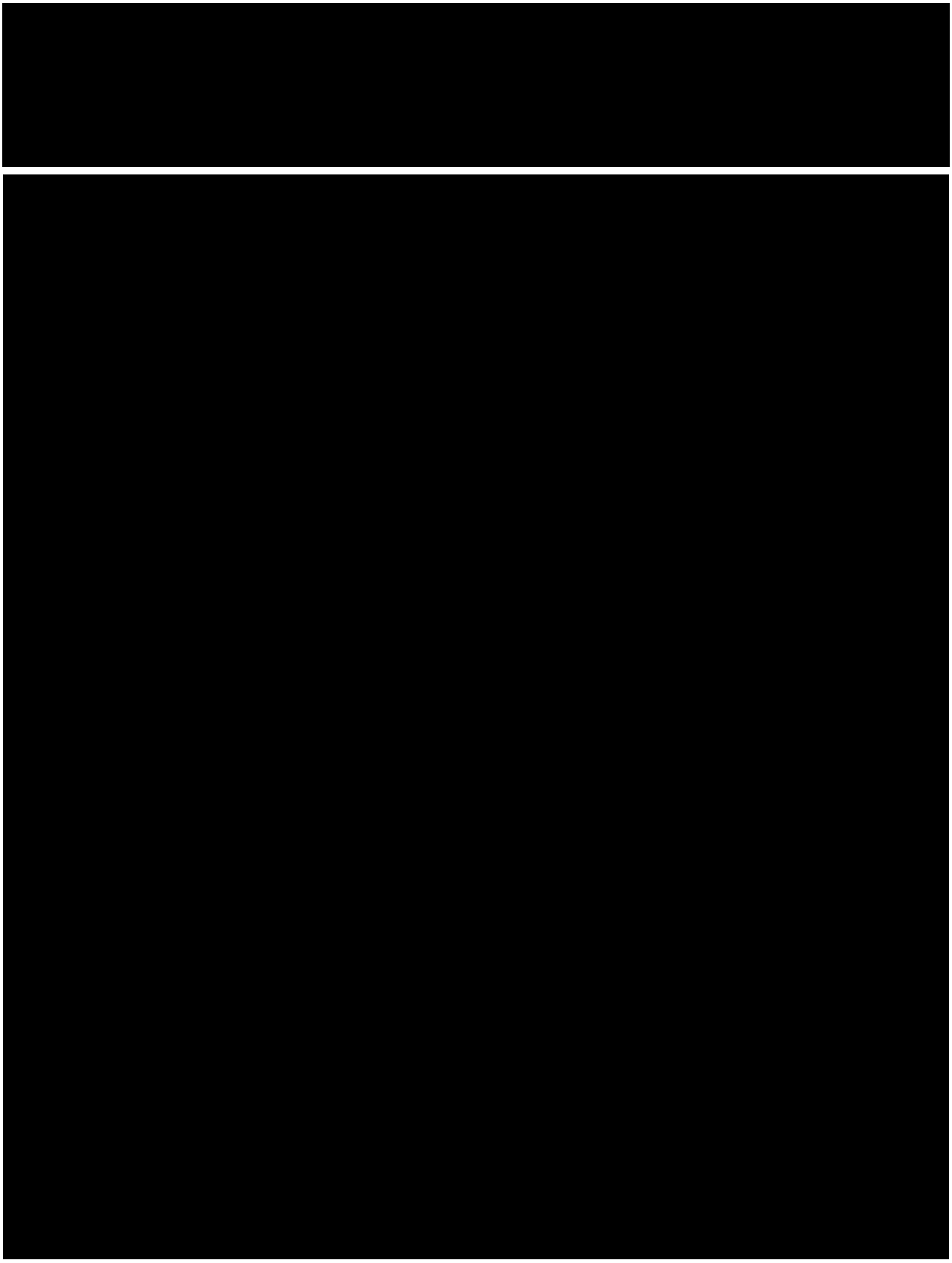
[redacted]

[redacted]

2.10 Patient-reported outcomes

Not Applicable.

[redacted]



[redacted]

2.13 Interim analysis

An interim analysis for futility will be implemented to allow possible termination of recruitment and the study in the event that there is insufficient efficacy. The patients for inclusion in the formal interim analysis for futility will be determined shortly after the 16th patient is enrolled in the FAS and the analysis will be conducted when this initial group of patients to be included in the analysis have at least 20 weeks of follow-up or have withdrawn early. However, any decision to stop or continue the study will be made based on all data available at the IA cut-off taking the futility analysis into account.

The futility criteria will be considered met if the observed overall response rate (ORR) assessed by central independent reviewer is less than or equal to 25% which is considered a threshold for clinical relevance. This will trigger consideration for stopping the study taking account of all available data and not just the response data required for determination of futility.

The choice of futility threshold has also taken account of operating characteristics which suggest that the chance of the futility criteria being met is high if the true underlying response rate is in a low range (e.g. <=20%); whereas if the true rate is considerably higher, as expected, then there is a very low chance of declaring futility at the IA. Full details of the futility criteria and operating characteristics are provided below in Table 2-15 Predictive probability of the lower bound of 95% CI exceeding 20% at the primary analysis under different interim results and Table 3-2 Operating characteristics with regard to the 95% CI excluding 20% response rate.

Futility criteria

Given the data observed in the IA, the probability of the lower bound of 95% CI at the primary analysis exceeding a certain response rate (e.g. 20%) conditional on the observed number of responders observed at the IA can be calculated. The conditional probability can be calculated using beta-binomial distribution (posterior predictive distribution). Let Y represent the number of responders from m future patients at the primary analysis and x is the number of responders among n patients at the interim analysis. The (posterior) predictive distribution of Y conditioned on the observed data at the interim analysis (x responders out of n patients) is a beta-binomial distribution described by

$$p(Y = y|x,n) = \binom{m}{y} \frac{B(a_0+x+y, b_0+n-x+m-y)}{B(a_0+x, b_0+n-x)}$$

where a minimally informative unimodal Beta distribution B(a0, b0) [Neuenschwander B, Branson M and Gsponer T. (2008)] is used with mean equal to 20%, i.e., the prior distribution will be Beta (0.25, 1) for the POS calculations at the interim analysis.

Table 2-15 Predictive probability of the lower bound of 95% CI exceeding 20% at the primary analysis under different interim results shows the predictive probabilities that the 95% CI excludes 20% at the primary analysis under different interim results. For example, with 16 patients at IA, if 4 responses are observed (i.e. 25% response rate), the probability of the 95% CI excluding 20% at the primary analysis is 13.7%.

Table 2-15 Predictive probability of the lower bound of 95% CI exceeding 20% at the primary analysis under different interim results

# of responses	Observed response rate at IA given n=16 (%)	Predictive probability that the 95% CI excludes 20% at the primary analysis (%)[a]
1	6.3	< 0.1
2	12.5	0.5
3	18.8	3.5
4	**25.0**	**13.7**
5	31.3	34.4
6	37.5	61.0
7	43.8	83.1
8	50.0	94.9
9	56.3	99.0

[a]The predictive probabilities are calculated from a beta-binomial distribution.

3 Sample size calculation

3.1 Primary analysis

Based on the exact binomial distribution, approximately 40 patients will be enrolled if the study is not stopped for futility at the time of the interim analysis. The exact 95% and 80% CIs for potential observed ORR for 40 patients are shown in Table 3-1.

The 95% CI, via the lower limit, is used to establish the levels of response which are exceeded by taking the combination therapy according to a robust standard of evidence (i.e. one-sided alpha=0.025).

Due to the uncertainties regarding the historical control data there is no specific “success” threshold level that we can apply that the lower limit should be greater than to give robust evidence that dabrafenib and trametinib combination therapy is better than historical control; however, the study sample size gives reasonable operating characteristics for an illustrative threshold historical level of 20%, which is higher than the range expected based on the information given in the literature (protocol section 1.1.3).

The study also aims to provide evidence that trametinib gives added value to the dabrafenib and trametinib combination over and above dabrafenib monotherapy treatment. Since a lower standard of evidence is usually required to show such added value, the lower limit of an 80%

CI is used to identify the response rates which will be exceeded by taking the combination therapy based on a reduced level of evidence (one-sided alpha of 0.1). Again it is difficult to ascertain a definitive threshold for "success" for evaluation in these circumstances but the number of patients in this trial give reasonable operating characteristics for an illustrative threshold level of 32%, which is the response rate observed in dabrafenib monotherapy patients in the study DRB436A2102 although based on limited data. Note that the 95% CIs can also be used to provide more robust evidence of the benefit of trametinib by looking at the lower limit compared to possible levels of dabrafenib monotherapy response.

Table 3-1 Exact binomial 95 and 80 percent confidence intervals around potential observed ORRs for N=40

Number of responders	Observed ORR (%)	95% exact CI (%)	80% exact CI (%)
12	30.0	16.6, 46.5	20.5, 41.2
13	32.5	18.6, 49.1	22.7, 43.8
14	35.0	20.6, 51.7	24.9, 46.3
15	37.5	22.7, 54.2	27.1, 48.9
16	40.0	24.9, 56.7	29.4, 51.4
17	42.5	27.0, 59.1	31.7, 53.9
18	45.0	29.3, 61.5	34.1, 56.3
19	47.5	31.5, 63.9	36.4, 58.8
20	50.0	33.8, 66.2	38.8, 61.2
21	52.5	36.1, 68.5	41.2, 63.6
22	55.0	38.5, 70.7	43.7, 65.9

For example, out of the 40 patients, with 14 responses (35%), the lower bound of 95% CI would be higher than 20%; with 18 responses (45%), the 80% CI would be higher than 32%; and with 20 responses (50%), the 95% CI would be higher than 32%.

Table 3-2 Operating characteristics with regard to the 95% CI excluding 20% response rate and Table 3-3 Operating characteristics with regard to the 95% and 80% CIs excluding 32% response rate show the operating characteristics under different true ORR with respect to different criteria. The tables show the probability of meeting the futility consideration criteria (e.g. less than 5 responders out of 16 patients), the probability of the confidence interval excluding the target response rate at the primary analysis, and the probability that the futility criteria is not met at IA but the confidence interval does not exclude the target response rate at the primary analysis.

At this sample size, when the true ORR is ≤ 20%,

- the probability of meeting the futility consideration criteria at interim analysis is > 79%,
- the probability of the 95% CI excluding 20% at the primary analysis is >1.6%,
- and the probabilities of the 95% CI and the 80% CI excluding 32% at the primary analysis are both < 0.1% respectively.

Within 40 patients, if the true ORR is 55% or higher, then

- the probability of meeting the futility consideration criteria at IA is < 2%,

- the probabilities of the 95% CI excluding 20% and the 80% CI excluding 32% at the primary analysis are both > 90% respectively,
- and the probability that the 95% CI excludes 32% is > 78%.

Table 3-2 Operating characteristics with regard to the 95% CI excluding 20% response rate

True ORR (%)	Probability to meet futility consideration criteria at IA (%)	Probability that the futility consideration criteria is not met at IA and the 95% CI excludes 20% at primary analysis (%)	Probability that the futility consideration criteria is not met at IA and the 95% CI does not exclude 20% at primary analysis (%)
20	79.8	1.6	18.6
25	63.0	8.5	28.4
30	45.0	25.2	29.8
35	28.9	49.1	22.0
40	16.7	71.7	11.6
45	8.5	87.1	4.4
50	3.8	95.0	1.2
55	1.5	98.3	0.2
60	0.5	99.5	< 0.1

The probabilities are calculated based on the exact binomial distribution.

Table 3-3 Operating characteristics with regard to the 95% and 80% CIs excluding 32% response rate

True ORR (%)	Probability to meet futility consideration criteria at IA (%)	Probability that the futility consideration criteria is not met at IA and the 95% CI excludes 32% at primary analysis (%)	Probability that the futility consideration criteria is not met at IA and the 95% CI does not exclude 32% at primary analysis (%)	Probability that the futility consideration criteria is not met at IA and the 80% CI excludes 32% at primary analysis (%)	Probability that the futility consideration criteria is not met at IA and the 80% CI does not exclude 32% at primary analysis (%)
20	79.8	< 0.1	20.2	< 0.1	20.1
25	63.0	0.1	36.9	0.5	36.5
30	45.0	0.6	54.4	3.1	51.9
35	28.9	3.6	67.5	12.1	59.0
40	16.7	12.9	70.5	30.5	52.9
45	8.5	31.4	60.1	55.2	36.3
50	3.8	56.0	40.1	77.6	18.5
55	1.5	78.5	20.0	91.7	6.8
60	0.5	92.4	7.1	97.8	1.7

The probabilities are calculated based on the exact binomial distribution.

3.2 Power for analysis of key secondary variables

Not applicable.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of date of last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year (yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of that specific record, if the imputed date is < start date of that record:

Use the start date of that record

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as ‘ongoing’ rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications, and for assigning pre/on/post treatment periods.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.3.1 Growth data

SDS will be calculated using the current formulae provided by the WHO as follows:

1. Calculate $z_{ind} = \frac{\left(\frac{X}{M}\right)^{L} - 1}{LS}$
2. If $|z_{ind}| \leq 3$, SDS = z_{ind}
   If $z_{ind} > 3$, SDS = 3 + (X – SD3*pos*) / SD23*pos*
   If $z_{ind} < -3$, SDS = -3 + (X – SD3*neg*) / SD23*neg*

where:

- *X* is height in centimeters or BMI in kilograms/m^2,
- *L*, *M* and *S* are height or BMI-, sex- and age-specific reference values from the WHO Growth Charts.

- SD3*pos* is the cutoff 3SD calculated by the LMS method:
  SD3*pos* = M * $(1 + LS*3)^{1/L}$
- SD3*neg* is the cutoff -3SD calculated by the LMS method:
  SD3*neg* = M * $(1 + LS*(-3))^{1/L}$
- SD23*pos* if the difference between the cutoffs 3SD and 2SD:
  SD23*pos* = M * $(1 + LS*3)^{1/L}$ - M * $(1 + LS*2)^{1/L}$
- SD23*neg* if the difference between the cutoffs -2SD and -3SD:
  SD23*neg* = M * $(1 + LS*(-2))^{1/L}$ - M * $(1 + LS*(-3))^{1/L}$

Height-for-age and BMI-for-age L, M and S reference values for males and females are available under http://www.who.int/childgrowth/standards/en/ (for patients aged between 0 to 5 years old) and http://www.who.int/growthref/en/ (for patients aged between 5 to 19 years old). These correspond to the latest available international references available at this time and described in the 2007 Bulletin of the World Health Organization (Mercedes de Onis et al 2007). The age category immediately above the patient's exact age should be used. SDS is actually a Z score that measures the distance from the population mean in units of standard deviations. That is, SDS < 0 refers to values lower than the population mean, and for example SDS ≤ -1.645 refers to values in the lowest 5%. (The usual percentiles most commonly used in the clinical practice can be derived from the z-score by a normal distribution).

Note that BMI is reported instead of weight as no reference data are provided by the WHO for age beyond 10.

Height velocity is defined as follows:

Height velocity (cm/6-months) = (height in time window *k* – height in time window *k-1*) ÷ ([assessment date in time window *k* – assessment date in time window *k-1*] x [365.25/2]),

and similarly for weight velocity.

Velocity SDS is calculated as (velocity – mean) / SD, where mean and SD are obtained as the height-, weight-, sex- and age-specific values (Baumgartner et al 1986), where the age category immediately above the patient's exact age (at the assessment date in time window *k*) should be used. Velocity SDS will only be calculated for time window *k* if data also exists for time window *k-1*, since calculating across multiple units of 6 months requires more than one reference value to be taken into account.

Table 5-3 summarizes the time windows for growth data, where windows are centered at every 6 months after start of study treatment. Although height and weight are collected more frequently than every 6 months (post-enrollment), this choice of time window length was made to reflect the degree of accuracy in the reference values (every 6 months) that will be used in the calculation of summary variables of growth.
In case of multiple assessments falling into the time window interval, the closest to the target date will be considered. For example, If we have 3 assessments falling under the time window of Day 85 to 252, then the closest one to target day of 168 will be considered. If two assessments are equidistant from target date, the average will be considered of those respective assessments.

Table 5-3 Time windows for growth data (height SDS, height velocity, weight velocity, BMI SDS)

Planned assessment	Time window
Baseline	Days ≤1
Month 6 (Day 168)	Days 85 – 252
Month 12 (Day 336)	Days 253 – 420
Month 18 (Day 504)	Days 421 – 588
Month xx (Day xx * 28)	Days ((xx – 3) * 28 + 1) – Day ((xx + 3) * 28)
Day 1 = date of first intake of study drug xx = Every 6 months	

5.3.2 Bone Age

Bone age SDS will be calculated as (bone age – chronological age) / SD) where the chronological age is the age in months at the time of the X-ray evaluation and SD is the sex- and age-specific standard deviation, as defined in the table below:

Table 5-4 Variability in Bone Age

Chronologic Age in Months	Boys SD	Girls SD
12	2.1	2.7
18	2.7	3.4
24	4	4
30	5.4	4.8
36	6	5.6
42	6.6	5.5
48	7	7.2
54	7.8	8
60	8.4	8.6
66	9.1	8.9
72	9.3	9
84	10.1	8.3
96	10.8	8.8
108	11	9.3
120	11.4	10.8
132	10.5	12.3
144	10.4	14
156	11.1	14.6
168	12	12.6
180	14	11.2
192	15	15
204	15.4	15.4

If the chronologic age falls between two values in the table above, the closest age should be used. If the chronologic age falls exactly in the middle between 2 values in the table above, then the age above the chronologic age should be used.

Table 5-5 Time windows for bone age SDS data

Planned assessment	Time window
Baseline	Days ≤1
Month 6 (Day 168)	Days 85 – 252
Month 12 (Day 336)	Days 253 – 420
Month 18 (Day 504)	Days 421 – 588
Month xx (Day xx * 28)	Days ((xx – 3) * 28 + 1) – Day ((xx + 3) * 28)
Day 1 = date of first intake of study drug xx = Every 12 months	

5.4 Statistical models

5.4.1 Primary analysis

Responses will be summarized in terms of percentage rates with 95% and 80% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413].

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI and exact one-sided p-value for the hypothesis test of the *null proportion* (0.10).

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used by changing **level** = "No". From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$LCL_{LEVEL="Yes"}\ (\%) = 100\% - UCL_{LEVEL="No"}\ (\%)$$

$$UCL_{LEVEL="Yes"}\ (\%) = 100\% - LCL_{LEVEL="No"}\ (\%)$$

Multiplicity adjustment

Not applicable.

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Secondary efficacy analysis

To analyze time to event endpoints (TTR, DOR, PFS and OS). An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. The TIME statement will include a variable with survival times and a (right) censoring variable with a value of 1, representing censoring. Kaplan-Meier survival and failure function estimates from this procedure will be used to construct the Kaplan-Meier figures.

Median survival will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-22.

Brookmeyer R and Crowley J. (1982)]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collet D (1994).].

5.4.4 Implementation of RANO guidelines (protocol Appendix 3)

As described in the protocol, the ORR will be evaluated by RANO criteria for solid tumors. This section provides some details on how to derive these endpoints by RANO and further details are included in the protocol Appendix 3.

The RANO criteria for assessment of LGG differs from that for HGG primarily in that LGG assessments utilize T2/FLAIR imaging while HGG assessments utilize Gadolinium enhanced imaging.

The major differences between RECIST 1.1 and RANO include:

- The measurability criteria for target lesion by RANO is based on two dimensions i.e two perpendicular diameters are measured for each target lesion;
- Corticosteroids use and clinical status are also considered for determining overall response;
- There are two types of non-target lesions by RANO: T1 enhancing non-target lesions and lesions on T2/FLAIR. Both types of non-target lesions contribute to the non-target lesion response.

Overall Lesion Response Collected on RANO eCRF page

In this study, Independent reviewer reported overall response and Investigator reported overall lesion response will be used for primary and secondary endpoints.For investigator, the overall response by RANO will be derived based on the collected overall lesion response on eCRF page "RANO Overall Lesion Response" (ZR domain, ZRCAT = "RESPONSE ASSESSMENT IN NEURO-ONCOLOGY", and ZRSCAT = "OVERALL LESION RESPONSE").

For independent reviewer, the overall response by RANO will be derived based on the collected overall lesion response on eCRF page "RANO Overall Lesion Response" (ZR domain, ZRCAT

= ”RESPONSE ASSESSMENT IN NEURO-ONCOLOGY”, and ZRSCAT = ”OVERALL RESPONSE”).

There will be two evaluations at a given assessment for independent reviewer i.e. primary RANO radiologic review without clinical data (read 1 – ZREVAL = “PRIMARY REVIEW”) and a secondary RANO review with clinical data (read 2 – ZREVAL = “SECONDARY REVIEW”). Secondary RANO review (read 2) with clinical data will be used for the primary endpoint of Best overall response per independent review. Primary review (read 1) will be used in supportive analyses based on radiographic review only, without clinical data.

Calculation of Overall Lesion Response by RANO

Overall lesion responses by RANO are also calculated from the following components:

1. Target lesion measurements;
2. Non-target lesion response;
3. New lesion present (Yes/No);
4. Corticosteroids use;
5. Clinical status.

All these components are collected on the following eCRF pages for investigator:

1. RANO target lesion - Measurable enhancing lesion (T1) (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”TARGET ENHANCING T1”);
2. RANO non-target lesion - Non-measurable enhancing lesion (T1) (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”NON-TARGET ENHANCING T1”);
3. RANO non-target lesion - Non-enhancing lesion (T2/FLAIR) (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”NON-TARGET NON ENHANCING T2/FLAIR”);
4. RANO New Lesion (ZI domain, ZICAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”NEW”);
5. Corticosteroids use and clinical status are collected on the Modified RANO Assessment (ZR domain, ZRCAT = ”MODIFIED RANO CRITERIA FOR BRAIN METASTASES”, ZISCAT = ”RESPONSE ASSESSMENT”).

All the above components are collected on the same eCRF pages for independent reviewer with the exception of ZICAT = ” RESPONSE ASSESSMENT IN NEURO-ONCOLOGY”.

Each target lesion by RANO criteria has two perpendicular diameters collected. In order to calculate the target lesion response, the product of the two perpendicular diameters is calculated for each target lesion. Then the sum of the products of diameters of all target lesions is compared to the baseline or nadir to determine the target lesion response.

The non-target lesion response is collected on the field of "Non-target lesion present" in the Modified RANO Assessment page, and is evaluated based on both non-target lesion eCRF pages as shown above.

The RANO response/progression criteria are summarized in Table 4-4.

Table 5-6 Summary of the RANO response criteria

	CR	PR	SD	PD
T1-enhancing disease	None	≥50% decrease from baseline	<50% decrease from baseline but <25% increase from nadir	≥25% increase from nadir*
T2/FLAIR	Stable or improved	Stable or improved	Stable or improved	Unequivocal PD*
New Lesions	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA**
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Worsened*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease
*: Progression occurs when this criterion is met
**: Not Applicable (NA): Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

5.5 Estimands

5.5.1 Primary estimand for the primary objective

The primary clinical question of interest is: what is the ORR by independent review as per RANO criteria for the combination treatment of dabrafenib + trametinib in children and adolescent subjects with BRAFV600 mutant relapsed or refractory HGG, regardless of study treatment discontinuation and before start of any new anti-neoplastic therapy.

The justification for the primary estimand is that it will capture the treatment effect of the study drug even after treatment is discontinued, but avoid potential confounding effects of any other new anti-neoplastic therapy.

The primary estimand is characterized by the following attributes:

1. Population: all subjects treated with BRAFV600 mutant relapsed or refractory HGG. Further details on the population are provided in protocol Section 5.
2. Primary Variable: BOR by independent review as per RANO criteria.
3. Treatment: dabrafenib plus trametinib, regardless of treatment discontinuation.

Handling of intercurrent events:

- **Discontinuation of study treatment for any reason:** Per treatment policy strategy, tumor assessment data collected after discontinuation of study treatment for any reason will be used to derive BOR.
- **Start of new anti-neoplastic therapy**: Per while on treatment strategy, tumor assessments collected before start of new anti-neoplastic therapy will be used to derive BOR. Tumor assessments collected on/after the start of new therapy will not be considered for evaluation of BOR.

Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria. See section 2.5.2 for details.

Sensitivity analyses for primary endpoint/estimand will be performed using the evaluable set, with all other aspects of the estimand as defined above. Additionally, analyses with response as assessed by the investigator (instead of by central review) will be done under the same estimand attributes.

5.5.2 Handling of missing values not related to intercurrent event

Subjects in FAS with unknown or missing BOR will be noted as such in the appropriate tables/listings and counted as non-responders in the analysis of ORR. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be "Unknown". If no valid post-baseline tumor assessments are available, the best overall response must be "unknown" unless progression is reported.

For the purpose of primary analysis, subjects with a BOR of "unknown" (UNK) will be treated as non-responders in estimating the ORR in the FAS.

5.5.3 Supplementary analysis

A supplementary analysis for the primary estimand will be done as defined below:

1. Population: all subjects treated with BRAFV600 mutant relapsed or refractory HGG. Further details on the population are provided in protocol Section 5.
2. Treatment: dabrafenib plus trametinib, regardless of treatment discontinuation or start of new anti-neoplastic therapy.
3. Variable: BOR by independent review as per RANO criteria.

Handling of intercurrent events:

- **Discontinuation of study treatment for any reason** - Per treatment policy strategy, tumor assessment data collected after discontinuation of study treatment for any reason other than PD will be used to derive BOR.
- **Start of new anti-neoplastic therapy**- Per treatment policy strategy, tumor assessment data collected after start of anti-neoplastic therapy will be used to derive BOR.

Summary measure: proportion of subjects with BOR of a confirmed CR or PR by independent review as per RANO criteria.

6 Reference

4. American Academy of Pediatrics. (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics, 114, 555-76.
5. Baumgartner RN, Roche AF, Himes (1986). Incremental growth tables: supplementary to previously published charts. American Journal of Clinical Nutrition, 43, 711-22.
6. Brookmeyer R and Crowley J. (1982) A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
7. Clopper CJ and Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
8. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
9. Fleming S, Thompson M, Stevens R, et al. (2011) Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 377: 1011-18.
10. Hummel TR., Wagner L, Ahern C., et al. (2013) A pediatric phase 1 trial of vorinostat and temozolomide in relapsed or refractory primary brain or spinal cord tumors: a children's oncology group phase 1 consortium study. Pediatr. Blood Cancer. 60: 1452-7.
11. Kalbfleisch JD and Prentice RL. (2002) The Statistical Analysis of Failure Time Data. Wiley Series in Probability and Statistics.
12. Lashford LS, Thiesse P, Jouvet A, et al. (2002) Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J. Clin Oncol. 24:4684-91.
13. Neuenschwander B, Branson M and Gsponer T. (2008) Critical aspects of the Bayesian approach to Phase I cancer trials. Statistics in Medicine, 27, 2420-2439.
14. Nicholson HS, Kretschmar CS, Krailo M, et al. (2007) Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer. 110:1542–1550.
15. Rijnbeek PR, Witsenburg M, Schrama E, et al. (2001) New normal limits for the paediatric electrocardiogram. Eur Heart J. 22: 702-11.
16. Ruggiero A, Cefalo G, Garre ML, et al. (2006) Phase II trial of temozolomide in children with recurrent high-grade glioma. J Neurooncol. 77:89-94
17. Smith B, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT and Forgue ST. (2000) Confidence Interval Criteria for Assessment of Dose Proportionality. Pharmaceutical Research, 17(10), 1278-83.
18. Warren KE, Gururangan S, Geyer JR, et al. (2012) A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: a Pediatric Brain Tumor Consortium study. J. Neurooncol.106: 643–649.

19. World Health Organization (WHO) Multicentre Growth Reference Study Group. (2009) WHO Child Growth Standards: Growth velocity based on weight, length and head circumference: Methods and development. Geneva: World Health Organization, http://www.who.int/childgrowth/en/.
20. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg. 1997;13:388-391.