NOVARTIS

Clinical Development

TMT212/Trametinib

MEK116540 (CTMT212X2101 / NCT02124772)

An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the MEK Inhibitor Trametinib in Children and Adolescents Subjects with Cancer of Plexiform Neurofibromas and Trametinib in Combination with Dabrafenib in Children and Adolescents with Cancers Harboring V600 mutation

Statistical Analysis Plan (SAP) Amendment 2 – final CSR

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22May2020	Prior DB lock	Amendment 1	Amendment 1	2.4.1 Study treatment/compliance *Duration of exposure to combination partner updated* 2.7 Analysis of secondary efficacy objective(s) *Analysis text updated to mention the analysis by disease cohort* *Also derivation of BOR and ORR updated for each disease cohort* 2.7.4 Supportive analyses *New section added* 2.8 Safety analysis *Updated the analysis text to mention the analysis by disease cohort* [redacted] Added the updated sections in document history. Updated as per sponsor comments.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
18Nov2020	Prior to DB lock	Amendment 2	Amendment 2	1 Introduction *Updated the SAP has been written in accordance with Novartis SOPs only* 1.1 Study Design *Clarified scope of the Addendum restricted to IA3 analysis only* 2.2 Analysis Set *Response Evaluation Population updated* 2.3 Patient disposition, demographics and other baseline characteristics *Central BRAF V600 mutation status* 2.3.1 Patient Disposition *Protocol deviations related to COVID-19 added* 2.4.1 Study treatment/compliance *Duration of exposure to combination partner updated* 2.7 Analysis of secondary efficacy objective(s) *Analysis text updated to mention the analysis by disease cohort* *Also derivation of BOR and ORR updated for each disease cohort* 2.7.4 Supportive analyses *New section added, Concordance analysis is described* 2.8 Safety analysis *Updated the analysis text to mention the analysis by disease cohort* 2.8.3 Safety analysis *Updated Hy's law definitions* [redacted]

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List of abbreviations

AE	Adverse Event
ADaM	Analysis Data Model
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BOR	Best Overall Response
CI	Confidence Interval
COVID-19	Coronavirus Disease-2019
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DI	Dose Intensity
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Easter Cooperative Oncology Group
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
IDMC	Independent Data Review Committee
ITT	Intent to Treat
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Medical Affairs
NCI	National Cancer Institutes
NF-1	Neurofibromatosis Type – 1
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PCI	Potential Clinical Importance
PD	Progressive Disease
[redacted]	[redacted]
PGx	Pharmacogenetics
PK	Pharmacokinetics
PN	Plexiform Neurofibromas
PR	Partial Response
PT	Preferred Term

RANO	Response Assessment in Neuro-Oncology
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SOP	Standard Operating Procedure
SRT	Safety Review Team
TBIL	Total Bilirubin
ULN	Upper Limit of Normal
WBC	White Blood Count

1 Introduction

This statistical analysis plan (SAP) details all planned analyses required for a Clinical Study Report (CSR) of study CTMT212X2101(MEK116540). This is a phase I/II study to evaluate safety, pharmacokinetics, pharmacodynamics and clinical activity of the MEK inhibitor trametinib in children and adolescent patients with cancer or plexiform neurofibromas and trametinib in combination with dabrafenib in children and adolescents with cancers harboring V600 mutations using an open label, dose-escalation design. This SAP will be used for the final analysis.

The content of this SAP is based on protocol MEK116540 (CTMT212X2101) amendment 09. The SAP has been written in accordance with Novartis SOPs only. All decisions regarding final analysis, as defined in this SAP document, have been made prior to Database Lock (DBL) of the study data.

1.1 Study design

This is a 4-part (Part A, Part B, Part C and Part D), Phase I/IIa, multi-center, open label, study in pediatric subjects with refractory or recurrent tumors.
Part A will be a pharmacokinetically driven limited dose escalation (i.e., 0.0125, 0.025 and 0.04 mg/kg/day) in subjects and will include an expansion for safety, tolerability, and pharmacokinetics (PK) in three age ranges (1 month to <2years, 2 to ≤12 years, and over 12 years of age). The primary goal of Part A is to establish the toxicity profile, PK, and recommended Phase 2 dose (RP2D) of trametinib in each age cohort. Approximately 18 subjects will be accrued to the dose escalation phase and 18 subjects to the age expansion phase.

> **Part A extension** will be an age-specific dose exploration in up to 12 subjects aged 1 month to < 6 years old. Preliminary PK analysis of pediatric patients in this current study suggests that for patients < 6 years old, an intermediate dose (i.e., 0.032 mg/kg/day) may increase the proportion of these patients who achieves exposures similar to adults. The goal of this additional dose exploration is to establish the safety, tolerability, PK and further refine the RP2D of trametinib in this younger age cohort.

Part B will be a tumor cohort expansion part of the study to further evaluate the safety, tolerability, and preliminary clinical activity of trametinib at the dose determined in Part A in tumor-specific pediatric populations. Disease cohorts are selected based on current data of proto-oncogene RAS (Ras)/ mitogen-activated protein kinase (MAPK) activation in childhood solid tumors. At least forty subjects are planned for Part B, 10 subjects in each of 4 disease cohorts.

- B1: Refractory or relapsed neuroblastoma
- B2:Recurrent or unresectable low grade gliomas associated with BRAF tandem duplication with fusion, or NF-1 subjects with gliomas, not suitable for the NF-1 with PN cohort
- B3:Neurofibromatosis Type -1 associated plexiform neurofibromas that are unresectable and medically significant.

- B4:BRAF V600 mutant tumors

Part C will be a limited dose escalation part of the study evaluating the combination of trametinib with dabrafenib in children and adolescents with recurrent, refractory or unresectable BRAF V600 mutated tumors. This part of the study will establish recommended Phase 2 doses (RP2D) of dabrafenib and trametinib when given in combination in children and adolescents. This part of the study will enroll approximately 18 subjects (including up to 6 adolescent subjects with BRAF V600 mutant metastatic melanoma) and will not open to accrual until the dose of dabrafenib in children is established in study BRF116013, the dose of trametinib is established in Part A and review of the available safety and PK data of trametinib and dabrafenib monotherapy in children is completed. Amendment 3 provides the updated safety data and dabrafenib dosing in children. Parts B and C may be open to accrual simultaneously. Patients who have had prior dabrafenib therapy may enroll in part C if they have had prior benefit to dabrafenib monotherapy, as determined by the investigator.

> **Part C extension** will be an age-specific dose exploration in 6 subjects aged 12 months to < 6 years old. If the trametinib dose of 0.032 mg/kg/day is tolerated in Part A extension, a combination of trametinib 0.032mg/kg/day and the full dabrafenib pediatric RP2D will be tested in this cohort. The goal of this additional dose exploration is to establish the safety, tolerability, PK and RP2D of the trametinib and dabrafenib combination in this younger age cohort

Part D will be a tumor cohort expansion part of the study to further evaluate the safety, tolerability, and preliminary clinical activity of the combination of trametinib and dabrafenib in tumor-specific pediatric populations listed below.

- D1: BRAF V600-mutant, relapsed or refractory low grade glioma (LGG)
- D2: BRAF V600-mutant, relapsed or refractory Langerhans cell histiocytosis (LCH)

Disease cohorts are selected based on current data of proto-oncogene RAS (Ras)/ mitogen-activated protein kinase (MAPK) activation in childhood solid tumors. Pediatric subjects 12 months to < 18 years of age are to be enrolled. Approximately 20 subjects with LGG and 10 subjects with LCH will be enrolled.

Subjects may not enroll in more than one part of the study. Subjects will receive study treatment until disease progression, death or unacceptable toxicity.

All parts of the study will use trametinib tablet strengths (0.125, 0.5, and 2 mg) for children who are able to reliably swallow tablets. In addition, an oral solution formulation (0.05 mg/mL) of trametinib is available. Doses will be calculated using body weight and prescribed using a dosing nomogram. Rules for dose modifications in response to toxicity are provided in the protocol.

For Parts C and D of the study, dabrafenib capsules (50 and 75 mg) or suspension or dispersible (10 mg/ml) will be used.

Three interim analyses (IAs) were performed for decision making of future development options and the data may be used for publication. No decision regarding the conduct of this study was made at IAs.

Final analysis will be performed when the last subject enrolled (without disease progression or withdraw from the study for another reason) has been in the study for a minimum of 12 months. This SAP amendment applies to final CSR analysis, as IA1, IA2 and IA3 were completed and stated in separate SAPs when this amendment was made.

1.2 Study objectives and endpoints

Objective	Endpoint	Hypothesis(es)
Primary		
To determine the safe and tolerable trametinib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures (Cτ) to the recommended adult dose	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state Cτ of trametinib	Infants, children and adolescents will tolerate doses of trametinib that achieve steady state trough concentrations associated with clinical benefit in adults
Secondary		
To characterize the pharmacokinetics of trametinib	Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and Cavg, as appropriate	

Objective	Endpoint	Hypothesis(es)
To characterize the safety and tolerability of trametinib	AEs; ECG; changes in laboratory values and vital signs	
To assess any preliminary anti-tumor activity of trametinib	Tumor response to trametinib as defined in [Appendix 3] through [Appendix 7 of protocol] will be assessed by investigator assessment.	
To determine the effect of covariates such as age and weight on the pharmacokinetics of trametinib using a population pharmacokinetics approach	CL/F, volume of distribution (V/F), absorption rate (ka), and coefficients for significant covariates	
To characterize the pharmacokinetics of trametinib and dabrafenib when administered in combination	Cτ (trough), AUC(0-t), AUC(0-τ), apparent clearance following oral dosing (CL/F) Cmax, tmax and Cavg of trametinib and dabrafenib when administered in combination, if the data permit	
To characterize the safety and tolerability of trametinib and dabrafenib when administered in combination	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs.	
To determine the safe and tolerable dabrafenib dose(s) when administered in combination with the recommended trametinib dose for chronic continuous daily dosing in pediatric subjects (infants, children and adolescents) that achieves similar exposures to the recommended adult dose	Adverse Events (AEs); ECG; ECHO; changes in laboratory values and vital signs. Steady state Cτ of trametinib; steady state AUC(0-12) of dabrafenib	
To assess any preliminary anti-tumor activity of trametinib and dabrafenib when administered in combination	Tumor response to dabrafenib and trametinib combination as defined in [Appendix 3] through [Appendix 7 of protocol] by investigator assessment.	
To determine the acceptability and palatability of trametinib and dabrafenib in pediatric subjects	Palatability questionnaire data	
[redacted]		

2 Statistical methods

2.1 Data analysis general information

Any interim and final analyses will be performed by a designated CRO ( ). SAS version 9.3 or later will be used to perform all data analyses and to generate tables, figures, and listings.

Data included in the analysis

The final analysis will be produced after all patients are considered to have completed the study, or if they discontinued the study treatment earlier, have completed post-treatment follow-up visit, or if they died while receiving treatment.

General analysis conventions

Pooling of center: 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 by study parts and by dose for Part A and Part C dose exploration, by age (< 2 years, 2 to < 6, 6 to <12, and 12 to 18 years) for Part A age expansion, by disease cohorts for Part B, and by tumor-specific cohorts for Part D, unless specified otherwise; 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, height, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by study parts and by dose for Part A and Part C dose exploration, by age for Part A age expansion, by disease cohorts for Part B, and by tumor-specific cohorts for Part D, unless specified otherwise.

Note for age the derivation will be as follows: round((date enrolled – birthdate +1)/ 365.25) to the nearest 0.1 decimal place.

Note for Pharmacokinetic reporting, age categorizations will be as follows: < 2 years, 2 to < 6, 6 to <12, and 12 to 18 years.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, study drug and study treatment will refer to the trametinib for Part A and Part B of the study. For Part C and Part D, study treatment will refer to dabrafenib and trametinib combination whereas the study drug will refer to each component of study treatment.

Date of first administration of study treatment

For Part A and Part B with trametinib monotherapy, the date of first administration of study treatment is defined as the first date when a nonzero dose of trametinib is administered and recorded on the Study Treatment (EXPOSURE) eCRF. The date of first administration of study treatment will also be referred as start of study treatment.

For Part C and Part D with dabrafenib and trametinib combination therapy, the date of first administration of study treatment is derived as the first date when a nonzero dose of any component of the study treatment (i.e. dabrafenib and trametinib combination therapy) was administered as per the Study Treatment (EXPOSURE) eCRF. (Example: if 1st dose of trametinib is administered on 03-JAN-2016, and 1st dose of dabrafenib is administered on 01-JAN-2016, then the date of first administration of study treatment is on 01-JAN-2016). 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

For Part A and Part B, the date of last administration of study treatment is defined as the last date when a nonzero dose of the study drug, trametinib, is administered and recorded on the Study Treatment (EXPOSURE) eCRF. The date of last administration of study drug will also be referred as end of study treatment.

For Part C and Part D, the date of last administration of study treatment is derived as the last date when a nonzero dose of any study drug was administered as per the Study Treatment (EXPOSURE) eCRF. (Example: if the last dose of trametinib is administered on 01-NOV-2016, and the last dose of dabrafenib is administered on 03-NOV-2016, then the date of last administration of study treatment is on 03-NOV-2016).

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 by:

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

- The date of the event (i.e. 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, etc.) is the start of the 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 case time of assessment and time of treatment start is captured (e.g. pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs, then an average of all the pre-dose values should be considered as baseline.

Baseline blood pressure measurements are performed in triplicate and is the average of the second and third measurements.

For the laboratory evaluation of creatinine, the average (mean) of multiple assessments on or before study treatment start is defined as "baseline".
If patients have no value as defined above, the baseline result will be missing.

Change from baseline

Change from baseline will be presented for safety data as described in Section 2.8.

Change from baseline is calculated as: For records occurring after baseline: (visit value) – baseline value.

If either the baseline or visit value is missing, the change from baseline is set to missing as well.

On-treatment assessment/event and observation periods

For safety summaries, the overall observation periods 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 31 after last administration of study treatment.

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 (vital sign, performance status, etc.) data collected over time (including unscheduled visits), the assessments will be time slotted. 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 worse of 2 assessments (i.e farthest outside the normal range) will be used. If multiple assessment are on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

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 etc.), all post-baseline values will be included (scheduled, unscheduled, repeat).

2.2 Analysis sets

All Treated Population

The All Treated Population is defined as all patients who received at least one dose of trametinib for Part A and Part B or at least one dose of any component of trametinib and dabrafenib combination for Part C and Part D. Baseline characteristics and anti-cancer activity will be evaluated based on this analysis population unless otherwise specified.

Safety Population

The safety population includes all patients who received at least one dose of trametinib for Part A and Part B or at least one dose of any component of trametinib and dabrafenib combination for Part C and Part D. All safety data will be analyzed using the Safety population. In this study, the All Treated population and Safety population are identical.

DLT Evaluable Population

The DLT evaluable population is defined as those subjects participating in dose determining portion of the study (Part A and 3+3 design portion of Part A extension, Part C and Part C

extension) fulfilling the 'All Treated' population criteria and having received an adequate treatment in the first 28 days to enable an appropriate evaluation of study treatment related DLTs. Adequate exposure during the first 28 days will be defined as having received >75% of planned study treatment doses (at least 21 doses), exclusive of missed doses due to treatment-related toxicity. Any patient in the 'All Treated' population who experiences a DLT, as defined in Section 3.2.3 of protocol, will also be included in the DLT evaluable population regardless of exposure. Subjects who are either withdrawn or dose reduced due to toxicity during the first 28 days will be included in the DLT evaluable population. Patients enrolled for only PK characterization (Part A extension, Part C, or Part C extension) or for the melanoma cohort in Part C will not be observed for DLTs.

Pharmacokinetic Population

The Pharmacokinetic Population will consist of all patients from the All Treated Population for whom a PK sample is obtained and analyzed and is evaluable. For a concentration to be evaluable, the following conditions are required:

- Patient receives one of the planned treatments
- Patient provides at least one primary PK parameter

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 pharmacokinetic population 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.

Response Evaluable Population

The Response-evaluable Population is defined as those subjects fulfilling the All Treated Population criteria with a pre-dose and at least one post-dose disease efficacy assessment (unless disease progression is observed before that time) or have discontinued for any reason. In addition, for patients evaluated by RANO criteria, their disease must be 'measurable' at baseline to be included in the Response-evaluable Population. This population will be used for sensitivity analysis on the efficacy endpoints. The sensitivity analysis will only be conducted in the final reporting effort.

Patient classifications:

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 2-1.

Table 2-1 Patient classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
All treated population	No written inform consent	No dose of study medication
Safety population	No written inform consent	No dose of study medication
DLT evaluable population	No written inform consent	Did not receive adequate treatment (>75% of planned study doses) in the first 28 days of study
Response Evaluable population	No written inform consent	No baseline tumor assessment. No post-baseline tumor assessments. No measurable disease at baseline for patients adhering to the RANO criteria
PK Analysis Set	No written informed consent	

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.

Third party data e.g. PK, [redacted] etc., collected in the clinical database without having obtained consent for collection will not be included in the analysis data sets. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroup of interest

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

- AEs, regardless of relationship to 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 (< 2 years, 2 - < 6 years, 6 -< 12 years, 12 to 18years)

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.

Summary tables will only be performed if at least 10% of patients or 10 patients are present in each subgroup. Some grouping of classes will be considered for age. 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

Unless otherwise stated, the All Treated population will be used for all baseline and demographic summaries and listings. All summaries and data listings in this section will be reported by dose level for Part A and Part C and by disease cohort for Part B and Part D. No inferential statistics will be provided

Basic demographic and background data

All demographic and baseline disease characteristic data will be summarized and listed by cohort and study treatment dose. Categorical data (e.g. gender, race, etc.) 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, etc.) will be summarized by descriptive statistics (N, mean, median, standard deviation, 25^{th} and 75^{th} percentiles, minimum and maximum). Body Surface Area (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. In addition, age will also be categorized and summarized by < 2 years, 2 - < 6 years, 6 -≤ 12 years, 12 to 18 years. Race and racial combinations will be summarized and listed.

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, details of tumor histology/cytology, histological grade, stage at initial diagnosis, time since initial diagnosis, time since last recurrence, and time since last progression.

A summary of disease burden at baseline will be produced. Metastatic disease at screening will be listed and summarized.
Summary statistics with frequency and its percentage will be tabulated for central BRAF V600 mutation status in subjects taking mono and combined therapies and also in LCH subjects.

Medical history

Medical history and ongoing conditions, including current and past cancer-related conditions and symptoms entered on the eCRF will be summarized and listed by cohort and study treatment dosage. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and by dose for part A and C, by cohort for Part B and Part D. 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 child bearing potential will be listed.

2.3.1 Patient disposition

A summary of patient status and reason for study withdrawal will be provided. This display will show the number and percentage of patients who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF. A listing of reasons for study withdrawal will also be provided.

A summary of study treatment status will be provided. This display will show the number and percentage of patients who are ongoing or discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date and reasons for study treatment discontinuation.

Protocol Deviations

The number (%) of patients in the All Treated population with any major protocol deviation will be tabulated by deviation category (as specified in the study protocol deviation plan). Major protocol deviations leading to exclusion from analysis sets will be tabulated separately. All protocol deviations will be listed. Similarly, a separate table and listing will be provided for protocol deviation related to COVID-19.

Analysis Populations

The number and percentages (based on the total number of patients in the All treated population) of patients in each analysis population (defined in Section 2.2) will be summarized by study part and by Part A doses, Part B cohorts, Part C doses, and Part D cohorts.

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

The safety population will be used for all summaries and listings of study treatment. All summaries and data listings in this section will be reported by study parts and by dose level for Part A, and Part C, and by disease cohort for Part B and Part D.

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized for trametinib by dose cohorts for Part A and disease cohorts for Part B. For Part C and Part D they will be summarized separately for dabrafenib and trametinib by dose cohorts for Part C and by disease cohorts for Part D). 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 trametinib monotherapy for Part A and Part B, and by dabrafenib and trametinib separately for Part C and Part D.

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

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to trametinib for Part A and Part B and to any combination partner for Part C and Part D.

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 last date of exposure to trametinib for Part A and Part B, and the latest of the last dates of exposure to any combination partner for Part C and Part D (see Table 2-2).

Summary of duration of exposure of study treatment will include categorical summaries based on <3 weeks, 3 weeks to 6 weeks, >6 weeks to 12 weeks, and >12 weeks intervals and using descriptive statistics (mean, standard deviation, etc.).

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

Scenario	Definition of last date of exposure of study drug	Example
Daily administration of the study drug	Date of last administration of a non-zero dose of the study drug.	Example: 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.

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.

For Part C and Part D, combined duration of exposure to study drug (*days*) = (the latest date of exposure to study drug) – (date of the earliest administration of study drug) + 1.

Summary of duration of exposure of each combination partner will include categorical summaries based on <3 weeks, 3 weeks to 6 weeks, >6 weeks to 12 weeks, and >12 weeks intervals and using descriptive statistics (mean, standard deviation, etc.).

Cumulative dose

Cumulative dose of the study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The planned cumulative dose for a study treatment component is the total planned dose as per the protocol up to the last date of investigational drug administration. 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 Study Treatment (EXPOSURE) eCRF.

For patients that 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 intensity and relative dose intensity will be summarized by age categories (<12 years and >=12 years for Dabrafenib, and <6 years and >=6 years for Trametinib.

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

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

Relative dose intensity
(RDI) is defined as follows: RDI = DI (mg/kg/day) / PDI (mg/kg/day).

In Parts A and Part B, DI and RDI will be summarized for trametinib monotherapy. Summary of RDI will include categorical summaries based on clinically meaningful intervals (<50%, 50-<75%, 75-<90%, 90-<110%, >=110%).

In study Part C and Part D, where there is combination therapy, DI and RDI will be summarized separately for each 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%).

Dose reductions, interruptions, permanent discontinuations or escalations

The number of patients who have dose reductions, escalations, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each study part as well as

study treatment components for combination therapies Part C and Part D. They will also be listed.

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, it will be counted as one interruption.

In addition, summaries of study treatment exposure and dose modifications (e.g., number of dose reductions, number of dose interruptions) will further characterize compliance.

2.4.2 Prior, concomitant and post therapies

2.4.2.1 Prior anti-cancer therapy

Prior anti-cancer therapy and anti-neoplastic therapy's medications will be coded using WHO coding dictionary; anti-neoplastic surgery will be coded using MedDRA. A summary of the number of prior anti-cancer therapy regimens will be produced and listed. 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 study parts and disease cohorts. 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, preferred term and study part. Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Details regarding MedDRA and most recent WHO coding dictionary will be included in the footnote in the tables/listings.

The above analyses will be performed using the All treated population.

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, Outputs will be summarized, and listed by dose for Part A, Part B, Part C, Part D, and by disease cohorts. The summary of concomitant medications will show the number and percentage of patients taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. 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.

In the summary of concomitant medications, each patient is counted once within each unique ingredient. For example, if a patient takes Amoxicillin on two separate occasions, the patient is counted only once under the ingredient "Amoxicillin". All concomitant therapies will be listed by dose level for Part A and Part C and by disease cohort for Part B and Part D. 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 population 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. All Treated Analysis Set) for those potentially affecting efficacy. According to the study protocol, certain treatment as listed in Protocol Section 9.2 (Prohibited Medications) 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

Part A

The primary objective of Part A is to determine the safe and tolerable trametinib dose(s) for chronic dosing in pediatric patients (infants, children, and adolescents) that achieves similar exposures (Cτ) to the recommended adult dose.

Part A extension: Based on preliminary PK data from Parts A, B and C, there was a trend for lower trametinib exposure in patients < 6 years old. An intermediate dose that is between the RP2D established in Part A and the higher dose that exceeded MTD will be explored. Safety, tolerability and PK are the primary endpoints of this part of the study.

Part B

Safety, tolerability and preliminary activity assessed by investigator are the primary endpoints of this part of the study.

Part C

The primary objective of Part C is safety, tolerability, and preliminary activity of the RP2D of trametinib in combination with a limited dose escalation of dabrafenib (50% of pediatric RP2D and 100% RP2D).

Part C extension: If Part A extension indicates trametinib 0.032mg/kg/day is tolerated in patients < 6 years old, the same trametinib dose will be explored in Part C extension with full dabrafenib RP2D. Safety, tolerability and PK are the primary endpoints of this part of the study.

Part D

Safety, tolerability and preliminary activity of dabrafenib and trametinib combination therapy assessed by investigator are the primary endpoints of this part of the study.

2.5.1 Primary endpoint

The primary endpoint for Part A (monotherapy), Part B (monotherapy), Part C (for trametinib and dabrafenib separately), and Part D (for trametinib and dabrafenib separately) is adverse events (AEs), ECG, ECHO, changes in laboratory values and vital signs. An additional primary endpoint specific to Part A is a steady state $C\tau$ of trametinib.

2.5.2 Statistical hypothesis, model, and method of analysis

No formal statistical hypotheses are being tested for any part of this study. For Part A and Part C, analysis of the data obtained from each part will be focused on comparison between dose cohorts and only descriptive methods will be utilized. For Part B and Part D, the objective response rate and the corresponding exact 95% CI will be reported by each disease cohort.

2.5.3 Handling of missing values/censoring/discontinuations

As the duration of treatment for a given patient will depend on efficacy and tolerability, the duration of follow-up will vary between patients. Consequently there will be no imputation for missing data.

Patients will be treated until disease progression, until the patient is no longer obtaining clinical benefit from continued treatment, unacceptable toxicity, the study is terminated, or the patient withdraws consent or begins a new therapy. Patients who withdraw from the study will be included in summaries up to the time of withdrawal, regardless of the duration of treatment.

Patients with the designation of treatment relationship for adverse events (AEs) and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”. There will be no other imputation for missing data other than what’s described in Section 5.3 for partial dates and for missing exposure end dates.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are to:

- To assess any preliminary anti-tumor activity of trametinib
- To assess any preliminary anti-tumor activity of trametinib in combination with dabrafenib

All efficacy analyses will be based on the All Treated population as defined in Section 2.2 unless otherwise specified. All analyses will be

summarized by dose levels in Part A, by disease cohorts in Part B, by dose levels in Part C, by disease cohorts for Part D, and by five disease cohorts listed below.

(1) Glioma Fusion subjects in Trametinib monotherapy

(2) BRAF V600 mutant glioma subjects in Trametinib monotherapy

(3) BRAF V600 mutant glioma subjects in combination therapy

(4) NF-1 with PN subjects in Trametinib monotherapy

(5) LCH subjects in combination therapy

Inclusion of patients in the 5 disease cohorts will be based on the enrollment criteria where available and applicable, and will be based on the genetic analysis.

2.7.1 Secondary endpoints

Overall Response Rate(ORR) by Disease Type

Overall Response Rate (ORR) is defined as the proportion of patients with best overall response (BOR) with confirmation of CR or PR according to criteria for a specific disease type, among patients with disease assessment at baseline. ORR will be calculated based on the All Treated population using investigator assessment of tumor response data and will be based on confirmed responses.

BOR for each patient is determined from the sequence of overall responses according to the following rules for RECIST 1.1, RANO, and Dombi criteria.

1. CR = at least two confirmed CR at least 4 weeks apart before progression
2. PR = at least two confirmed PR or better response at least 4 weeks apart before progression and not qualifying for a CR.
3. SD = requires at least one SD assessment or better determined at or beyond 12 weeks from randomization before progression, and not qualifying for CR or PR.
4. PD = progression after start of study treatment and not qualifying for CR or PR or SD
5. UNK = all other cases (i.e., not qualifying for confirmed CR or PR and without SD at or beyond 12 weeks or progression).

Neuroblastoma
Response evaluations for patients with neuroblastoma can include measurable disease (by CT/MRI alone) or Evaluable Disease (MIBG alone) and/or in combination with bone marrow, biochemical (urine HVA/VMA).

Response criteria for neuroblastoma patients with measurable disease as a component of their disease burden at enrollment will have measurable disease assessed according to RECIST v1.1, as well as evaluable disease assessments, to determine overall response.

Response criteria for neuroblastoma patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response.

Response criteria from neuroblastoma patients who have bone marrow responses are determined by Haematoxylin and Eosin (H&E) staining of bilateral bone marrow biopsies and aspirates.
If patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the ORR determination.

Refer to Appendix 4 in the Protocol for additional information.

Low Grade Glioma Patients

Anti-tumor activity for glioma patients will be assessed using Response Assessment in Neuro-Oncology (RANO) criteria with solid tumors through MRI. All measurable and non-measurable lesions should be assessed using the same techniques as at baseline.

Refer to Appendix 5 in the Protocol for additional information.

NF-1 Associated PNs
Response will be assessed using Dombi criteria at the time that follow-up MRI scans are performed as outlined in Section 7.1 of the Protocol.
Refer to Appendix 6 in the Protocol for additional information.

LCH Patients
Response criteria is adapted from Histiocyte Society Evaluations and Treatment Guidelines, April 2009 and is used in combination with RECIST criteria v1.1.

In the case of LCH patients, the ORR is the number of patients deemed to have treatment response (CR+REG) relative to the total number of patients treated in that cohort as described in Appendix 3 of the Protocol

Refer to Appendix 7 of the Protocol for more information.
BOR for each patient is determined from the sequence of overall responses according to the following rules for LCH subjects.

1. Complete resolution (CR)/Non-active disease (NAD) = at least two confirmed CR/NAD at least 4 weeks apart before progression
2. Regressive (REG) = at least two confirmed REG or better response at least 4 weeks apart before progression and not qualifying for a CR/NAD.
3. SD = requires at least one SD assessment or better determined at or beyond 12 weeks from randomization before progression, and not qualifying for CR/NAD or REG.
4. PD = progression after start of study treatment and not qualifying for CR/NAD or REG or SD

5. UNK = all other cases (i.e., not qualifying for confirmed CR or REG and without SD at or beyond 12 weeks or progression).

All Other Solid Tumors

Tumor response will be assessed using RECIST version 1.1 for patients with solid tumors except neuroblastomas, primary central nervous system tumors (gliomas), or PN(s).

Tumor assessments performed before the start of any further anti-cancer therapy (i.e. any additional secondary anti-cancer therapy or surgery) will be considered in the assessment of BOR. If a patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the ORR determination.

Note that if a patient shows at least one Non-CR/Non-PD (NN) assessment determined at or beyond 12 weeks from randomization and not qualifying for CR, PR, SD, or PD, then BOR for the patient is NN.

ORR is defined as the proportion of patients with best overall response (BOR) with confirmation of CR or PR according to criteria for a specific disease type, among patients with disease assessment at baseline

BOR with confirmation and ORR will be summarized for all disease types by therapy (monotherapy or combo-therapy) and by study part and dose based on the All treated population. Where appropriate, the lesion data will be listed for each patient.

A figure of percent change at maximum reduction from baseline in tumor measurement will also be provided, where appropriate.

As sensitivity analyses, response data may also be summarized based on response-evaluable population. As supportive analyses, for LGG and NF-1 with PN patients, the response data assessed by independent review assessment will also be summarized based on the All treated population.

2.7.2 Statistical hypothesis, model, and method of analysis

The primary analysis of response data will be performed on the All treated population by investigator assessment. Point estimate and exact confidence intervals (CIs) of ORR will be provided by disease type and by trametinib monotherapy and dabrafenib plus trametinib combination therapy, as well as by study part and dose.

2.7.3 Handling of missing values/censoring/discontinuations

Dates associated with response

For each disease assessment after baseline, determine a date associated with the response. For complete response (CR) and partial response (PR), assign to the latest date within the disease assessments. For stable disease (SD), Non-CR/Non-PD or Not Evaluable, assign to the earliest date within the disease assessments. For progressive disease (PD), assign to the earliest assessment date associated with the progression.

Unknown or Missing Tumor Assessments

Patients with unknown or missing best overall response (BOR) will be counted as non-responders. 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 All Treated Analysis Set and will be counted as 'failures'.

2.7.4 Supportive analyses

ORR by independent review assessment

The analyses of ORR will be repeated by independent review for LGG cohorts. For LGG patients, this incorporates the radiographic data which includes the lesion measurements from target lesions, non-target lesions, new lesion, corticosteroid status, and clinical status per old RANO (2010) and new RANO (2017). Please refer to the Protocol Appendix 5.

Waterfall plot will be presented for the analysis. Waterfall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall graphs. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph will be shown. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

Concordance analysis of ORR

Concordance analysis of ORR for LGG cohorts will be performed for assessment of the best overall responses by investigator and independent reviewer per old RANO (2010) and new RANO (2017). Concordance rate of ORR is calculated as Percent Agreement for responders and non-responders.

2.8 Safety analyses

Unless otherwise specified, all the DLT safety analyses will be based on the safety population as defined in Section 2.2 and summaries will include all events or assessments collected during the study. For all other safety analyses (i.e. AE, ECG, Labs, Vitals, etc.) they will be summarized by dose levels in Part A, by disease cohorts in Part B, by dose levels in Part C, by disease cohorts for Part D, and by five disease cohorts listed below.

(1) Glioma Fusion subjects in Trametinib monotherapy

(2) BRAF V600 mutant subjects in Trametinib monotherapy

(3) BRAF V600 mutant subjects in combination therapy

(4) NF-1 with PN subjects in Trametinib monotherapy

(5) LCH subjects in combination therapy

2.8.1 Adverse events (AEs)

AEs will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary). The latest available MedDRA version at the time of the analyses will be used. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE eCRF page will be listed along with 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 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 adverse event summaries will be produced by dose for Part A and Part C dose exploration, by disease cohorts for Part B, by tumor-specific cohorts for Part D, by age group (< 2 years, 2 to < 6, 6 to 12, and 12 to 18 years) for monotherapy (Part A and Part B combined) and combination therapy (Part C and Part D combined) ;

- overview of adverse events
- Overview of deaths and SAEs,
- AEs by SOC, PT and severity (post-text)
- AEs by SOC and severity (in-text)
- AEs by PT and severity (in-text)
- AEs suspected to be related by SOC, PT and severity (post-text),
- AEs suspected to be related by PT and severity (in-text),
- SAEs by SOC, PT and severity (post-text)
- SAEs by PT and severity (in-text)
- AEs leading to study treatment discontinuation by SOC, PT and severity (post-text)
- AEs leading to study drug discontinuation by PT and severity (in-text),
- AEs leading to dose reductions, leading to dose interruptions, and leading to fatal outcome (post-text).

- AESIs (in-text)

A summary of serious and non-serious adverse events with number of occurrences will be produced as per EudraCT requirements.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables for on-treatment adverse event which are not SAE's with an incidence greater than and equal to 5% and on 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.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Dose Limiting Toxicity

An AE will be considered a DLT if it is considered by the investigator to be at least possibly related to study treatment, meets any of the criteria listed in Section 3.2.3.1 or Section 3.2.3.2 of protocol and occurred during the first 28 days of treatment in the dose determining portion of the study (Part A and 3+3 design portions of Part A extension, Part C and Part C extension).

DLTs will be listed and summarized for age and the dose determining portion of Part A and Part C. Only the first cycle (28 days) of treatment will be considered when summarizing data regarding the dose limiting toxicities. The table will display the number of DLT's at each dose level. AE summary of DLTs will also be presented.

Note that isolated clinical laboratory value(s) considered **not** clinically significant by the investigators are not AEs and therefore, would not be DLTs.

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to compound, 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. The events considered as AESI's will be based off of the latest CRS.

Summaries of these AESIs will be provided by trametinib and dabrafenib, by dose and study part, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death 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

In the event that a patient has withdrawn consent, no data after the withdrawal of consent date from this patient including death is supposed to appear in the database, which should be part of the data cleaning process.

Separate summaries for on-treatment and all deaths will be produced by study part, system organ class and preferred term.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

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 study part):

- Worst post-baseline CTCAE grade (regardless of baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst post-baseline value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high classification to compare baseline to the worst post-baseline value.
- Trends of lab parameter values over time (baseline and selected on-treatment time points) 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 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

For laboratory tests (e.g.potassium, sodium, calcium, glucose, magnesium, hemoglobin and lymphocytes) 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.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of patients with non-missing value at each particular visit.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), 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:

- AST or ALT > 3 x Baseline
- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
    - TBL> 2 x Baseline
    - TBL > 2xULN
    - TBL > 3xULN
    - ALT or AST > 3xULN & TBL > 2xULN
    - ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN
    - [AST or ALT > 3 x Baseline] & [TBL> 2 x Baseline AND TBL > 2.0 x ULN]
    - [AST or ALT > 8.0 x ULN] & [TBL> 2 x Baseline AND TBL > 2.0 x ULN]
    - Lower ([AST or ALT > 3 x Baseline] OR [AST or ALT > 8.0 x ULN]) & [TBL> 2 x Baseline AND TBL > 2.0 x ULN]

A clinically significant liver safety signal corresponding to Hy's Law events are defined as a patient with abnormal ALT or AST baseline value and combined elevations post baseline (based on the peak values at any post-baseline time for a patient). [AST or ALT > 3 x Baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower and combined with [TBL> 2 x Baseline AND TBL > 2.0 x 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

The number and percentage of patients with notable ECG values at scheduled assessments will be presented by Parts A, B, C, and D.

- QTcB
  - 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 2-7 Recommendation for normal heart rate per age group and gender. The number and percentage of patients with notable values will be presented.

Table 2-7 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 provided and notable values will

be flagged. In the listing, the assessments collected outside of on-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 of the 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 QTcB 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.

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.

2.8.4.2 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 at each scheduled assessment time and by 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 **absolute change from baseline** will be categorized as follows:

- Any increase
- No change
- Any decrease:
  - 0 - <10% decrease
  - 10 - <20% decrease
  - ≥20% decrease
- ≥10% decrease and ≥ Lower Limit Normal (LLN)
- ≥10% decrease and < LLN

- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

A listing of all LVEF assessments will be provided including patient level details of absolute change from baseline. Assessments collected outside of on-treatment period will be flagged.

2.8.5 Vital signs

The following parameters will be collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), respiration rate (breathes/min), systolic and diastolic blood pressure (mmHg).

Data handling

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

The baseline blood pressure is the average of the systolic and average of the diastolic measurements.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-9.

Table 2-9 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Body temperature	>= 38.5	≤ 35.0

The number and percentage of patients with notable vital sign values (high/low) will be presented as described in Section 2.8. Shift tables for vital sign values will also be presented.

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 cohorts and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.5.1 Karnofsky and Lansky Performance Status

Data handling

The Karnofsky and Lansky PS scale (see Appendix 1) will be used to assess physical health of patients, ranging from 10 (least active) to 100 (most active).

Data analysis

Frequency counts and percentages of patients in each score category of 100, 90, 80, 70, and < 70 will be provided by cohorts and age groups at baseline and at each scheduled post-baseline visit. A patient will be reported only in the age group set at baseline. A summary of change from baseline by scheduled visits as well as the worst case post-baseline and the best case post-baseline changes during the study will be performed.

A supporting listing will also be provided.

2.8.5.2 Palatability

Palatability assessments (bitterness, sweetness, texture and overall taste) will be listed for each patient receiving oral liquid formulation (i.e. trametinib solution or dabrafenib suspension) and summarized by assessment time. The number and percentages of patients for each category of palatability assessments will be summarized.

2.8.5.3 Physical Examination

Dermatologic skin assessments, radiograph of wrist and tibial growth plate, and ophthalmologic examination will be listed for each patient at each time point.

In addition, tanner staging will be listed for each patient at each time point.

2.8.5.4 Cardiovascular Events

Cardiovascular events will be listed for all patients in which an event occurred.

2.8.5.5 Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If patients become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

2.9 Pharmacokinetic endpoints

Pharmacokinetic analyses will be conducted based on the PK population unless otherwise specified.

PK parameters

PK parameters for trametinib, dabrafenib and dabrafenib metabolites will be calculated based on non-compartmental methods using Phoenix WinNonlin version 5.2 or higher (Pharsight, Mountain View, CA). All calculations of non-compartmental parameters will be based on actual blood sampling times. PK parameters listed in Table 2-10 will be estimated and reported as data permit.

Population PK parameters may include the following and are dependent upon the final population PK model for both trametinib and/or dabrafenib: apparent clearance following oral dosing (CL/F), central volume of distribution (Vc/F), absorption rate constants (ka) and MTIME (time when absorption rate changes).

Final PK parameters will be summarized and will be compared to historical adult data.

Table 2-10 PK parameters

AUClast	The AUC from time zero to the last measurable plasma concentration sampling time (tlast) ($ng*hr*mL^{-1}$)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (after repeated dose). The plasma concentration at 12 or 24 hours after dosing will be set equal to the predose plasma concentration for the calculation of AUCtau
Cmax	The maximum (peak) observed plasma concentration following a single dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma concentration following a single dose administration (hr)
CL/F	The total apparent body clearance of drug from plasma ($L*hr^{-1}$)
Ctrough	The observed plasma concentration just prior to the beginning of, or at the end, of a dosing interval
Cavg	The average steady-state plasma concentration will be calculated as the ratio of AUCtau (where tau = 24 h for trametinib and 12 h for dabrafenib), as data permit

For Part A and Part A extension, PK parameters will be summarized by day and dose level. Additionally, PK parameters will be summarized by age categories (<2 years, 2-<6 years, 6-<12 years,12 to 18 years) for each dose cohort.

For Part B, PK parameters will be summarized by day, dose and disease cohort. Additionally, PK parameters will be summarized by age categories (<2 years, 2-<6 years, 6-<12 years, 12 to 18 years)for each disease cohort.

For Part C and C extension, PK parameters for trametinib, dabrafenib and dabrafenib metabolites will be summarized by day and combination regimen(e.g. TMT 0.0025mg/kg+DRB 2.25 mg/kg). Additionally, PK parameters will be summarized by age categories (<2 years, 2-<6 years, 6-<12 years, 12 to 18 years) for each combination regimen.

For Part D, PK parameters will be summarized by day, dose and disease cohort. Additionally, PK parameters will be summarized by age categories (<2 years, 2-<6 years, 6-<12 years, 12 to 18 years) for each disease cohort.

Descriptive statistics for trametinib, dabrafenib and dabrafenib metabolites (n, arithmetic mean, CV% mean, standard deviation (SD), median, geometric mean, CV% geo-mean, minimum and maximum) will be presented for all PK parameters, except Tmax, where only n, median, minimum and maximum will be presented.

All individual PK parameters will be listed by study part and treatment.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) will be presented for trametinib, dabrafenib and dabrafenib metabolite concentration at each scheduled time point by study part, day, and treatment dose .

Individual concentration-time profiles for trametinib, dabrafenib and dabrafenib metabolites with median will be displayed graphically by study part, day and treatment for All treated population on semi-log view. In addition, the median/geometric mean concentration-time profiles for trametinib, dabrafenib and dabrafenib metabolites will be displayed graphically by study part, day and treatment for PK population on linear and semi-log view.

All individual plasma trametinib, dabrafenib and dabrafenib metabolite concentrations will be listed by timepoint and summarized by study part, planned sampling time, treatment day and treatment.

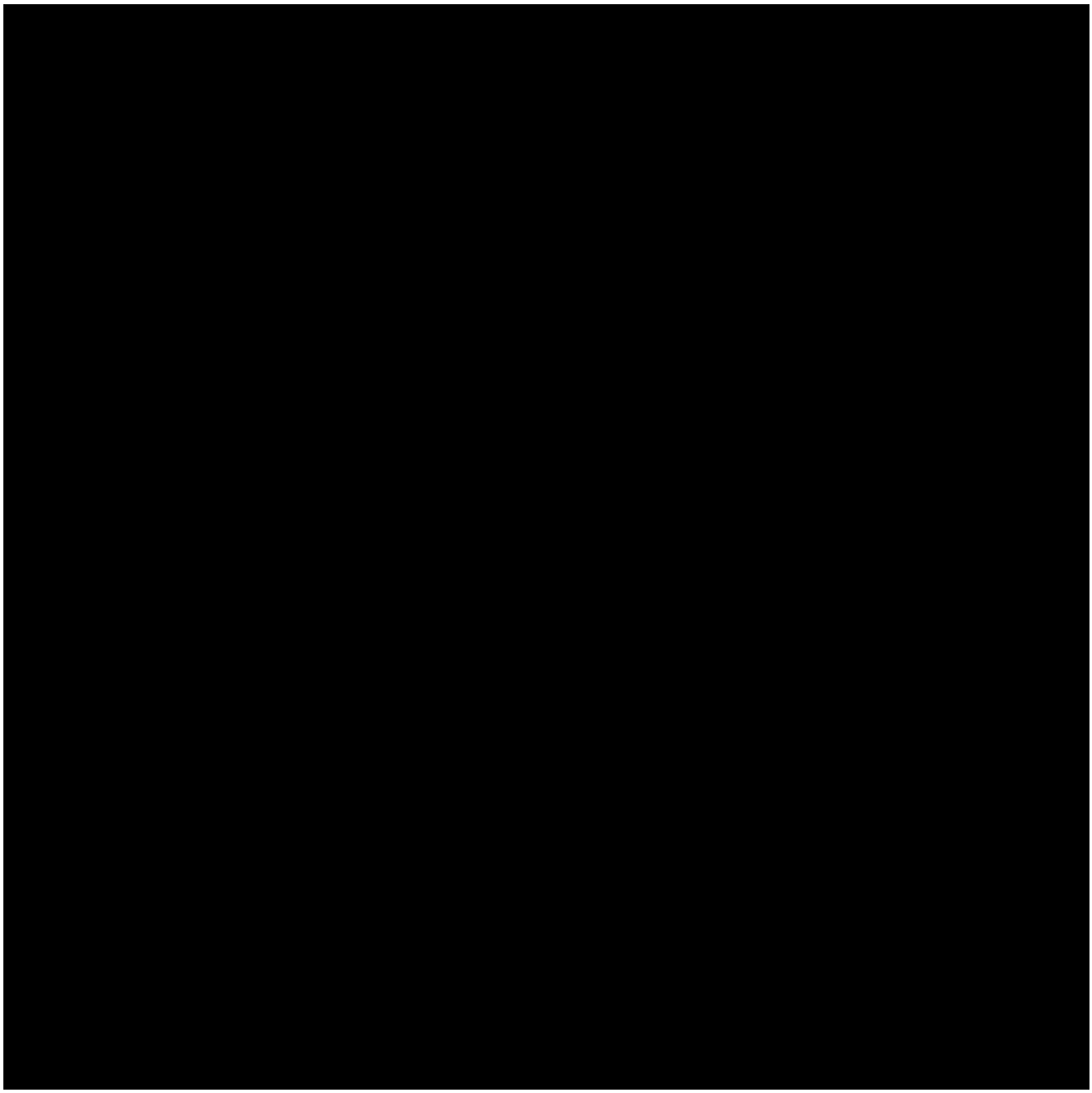
Handling of PK data below LLOQ or missing

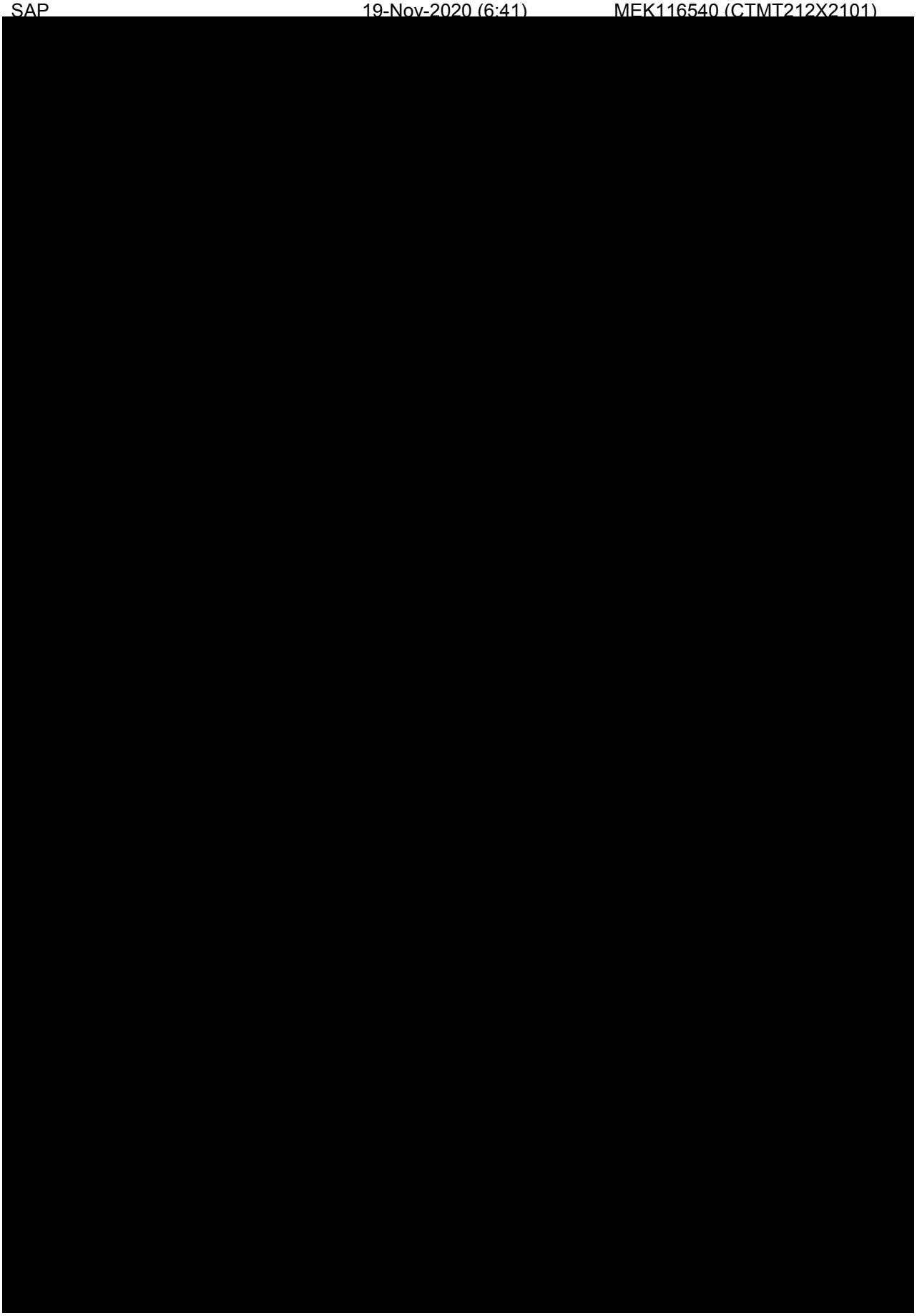
All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

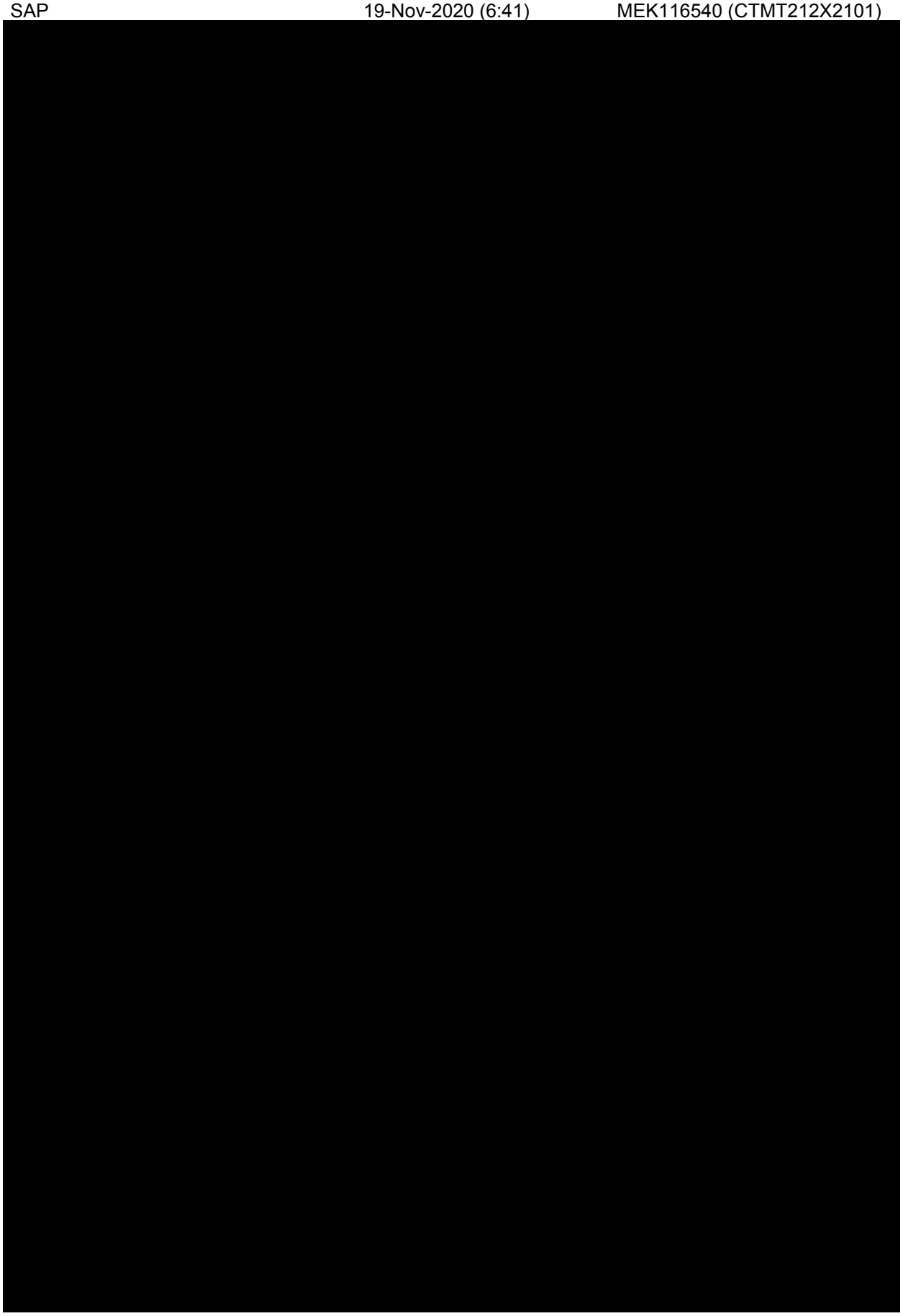
Missing values for any PK data will not be imputed and will be treated as missing.

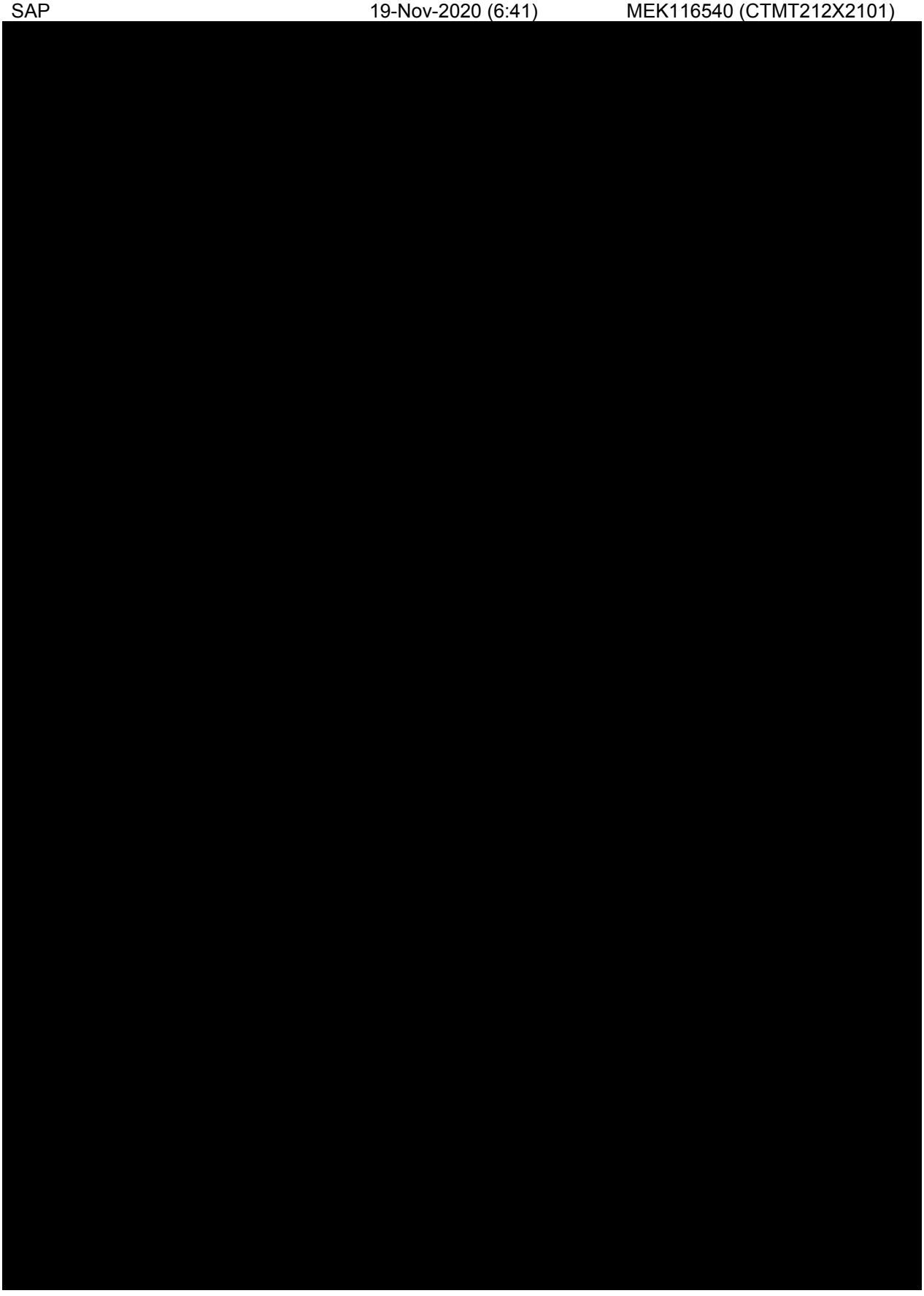
Population Pharmacokinetic Analysis

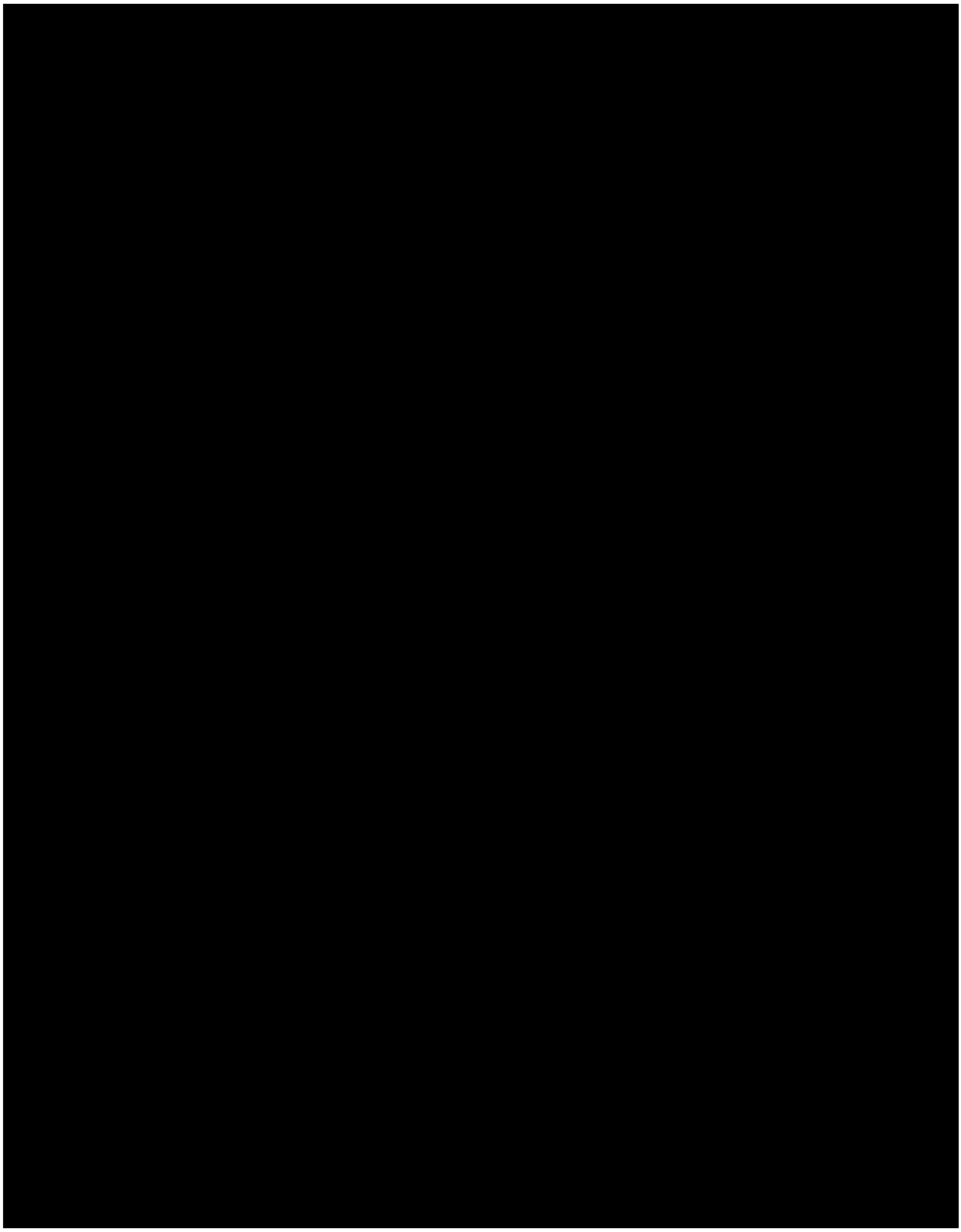
All trametinib and dabrafenib concentration-time data may be combined and included in a population PK analysis that will examine the influence of demographics (especially age and weight) on the PK of study treatment. Trametinib and dabrafenib PK parameters estimated in the population PK analysis will include: apparent oral clearance (CL/F), central volume of distribution (Vc/F) and absorption rate constants (ka) (trametinib only). Data may be pooled with PK data from adult studies. These analyses will be documented in a separate analysis plan, and the results will be reported in a separate population PK report outside of the CSR.











2.11 Interim analysis

Part A - Trametinib Dose-Escalation and Age Group Expansion

No interim analysis is planned for Part A, safety and PK data will be examined on an ongoing basis to support dose escalation decisions. Prior to determining the dose for the next cohort enrolled, [redacted] the Cτ at steady state.

Part B - Tumor-specific Expansion Cohort

An interim analysis is planned after all subjects have been enrolled in B3, NF-1 with PN cohort and have completed at least 3 post treatment assessments (Weeks 17, 33 and 49) or have discontinued treatment earlier. The results will be used for decision making for future development options and may be used for publications. At this time, no statistical hypothesis testing is planned, and no decision regarding the conduct of this study will be made.

At this interim analysis, all data collected at the time of the data cut-off for the interim analysis will be analyzed. In addition, safety and tolerability will be monitored closely on a continued basis.

Part C – Combination Cohort

Prior to opening Part C the available safety and PK data from Parts A will be reviewed. Safety and PK data will be examined on an ongoing basis to support dose escalation decisions. Prior to determining the dose for the next cohort enrolled, [redacted]

Part D – Expansion Cohort with Combination Therapy

An interim analysis is planned after all subjects have been enrolled in LGG cohort and have completed at least 12 months of treatment or have discontinued treatment earlier. The results will be used for decision making for future development options and may be used for publications. At this time, no statistical hypothesis testing is planned, and no decision regarding the conduct of this study will be made.

At this interim analysis, all data collected at the time of the data cut-off for the interim analysis will be analyzed.. In addition, safety and tolerability will be monitored closely on a continued basis. A separate TOC will be added as an appendix for the interim analysis reporting effort.

3 Sample size calculation

Part A - Trametinib Dose-Escalation and Age Group Expansion

The total number of patients to be enrolled in Part A will depend on the number of patients needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, it is anticipated that approximately 48 patients will be enrolled.

Given true incidence rates of DLTs, the associated probability of escalating to the next dose level in a 3+3 scheme are provided for reference below in Table 3-1 3-1.

Table 3-1 Statistical Basis for Phase I Dose Escalation in a 3+3 Scheme

True incidence of dose-limiting toxicity	10%	20%	30%	40%	50%	60%
Probability of escalating the dose	0.91	0.71	0.49	0.31	0.17	0.08

Part B - Tumor-specific Expansion Cohort

The sample size for Part B is based on feasibility, practicality, and what would be sufficient for the characterization of the safety of trametinib and the plasma PK for the populations enrolled. Each of the 4 expansion cohorts will enroll at least 10 evaluable patients, 5 patients in each cohort will be under the age of 6 years. Therefore, an estimated of at least 40 patients will be enrolled into Part B.

If less than 1 response is observed after x10 patients complete the study, the treatment could be considered to have insufficient clinical activity in that cohort. The estimated sample size (n=10) for the Part B expansion cohorts was further evaluated using exact binominal distribution probabilities (Clopper CJ, et al.), and the details are provided in Table 3-2 and Table 3-3.

For example, if zero responses are observed among 10 patients in a cohort [if the response rate (RR)=5%], the chance of declaring the cohort as having insufficient clinical activity after 10 patients is 60%. If the true RR=15% for trametinib in unresectable low grade gliomas patients, the chance approximately 20%. Table 3-2 provides the corresponding 95% CIs around potential observed objective response rates given N=10 subjects. Table 3-3 provides the corresponding 95% CIs around potential observed objective response rates given N=10 subjects.

Table 3-2 Exact Binomial Probabilities of Observing 0 and 1 (or more) Responses in 10 Subjects

True RR	Probability of Observing 0 responses in 10 Subjects	Probability of Observing ≥1 Responses in 10 Subjects
5%	0.60	0.40
10%	0.35	0.65
15%	0.20	0.80
20%	0.11	0.89
25%	0.056	0.94
30%	0.028	0.97

Table 3-3 Exact Binomial Probabilities of Observing 0 and 1 (or more) Responses in 10 Patients

Observed Objective Response Rate	Exact 95% Confidence Interval (%) (N=10)
10%	0.3, 44.5
20%	2.5, 55.6
30%	6.7, 65.2
40%	12.2, 73.8
50%	18.7, 81.3
60%	26.2, 87.8
70%	34.8, 93.3

Part C – Combination Cohort

The total number of patients to be enrolled in Part C will depend on the number of patients needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, it is anticipated that approximately 18 patients will be enrolled.

Part D – Expansion Cohort with Combination Therapy

The sample size for Part D is based on feasibility, practicality, and what would be sufficient for the characterization of the safety and preliminary anti-tumor activity of trametinib/ dabrafenib combination and the plasma PK for the populations enrolled. At least 20 subjects with LGG and at least 10 subjects with LCH will be enrolled. Therefore, it is estimated that at least 30 subjects will be enrolled into Part D.

The estimated sample size for the LGG and LCH cohorts in Part D is further evaluated using exact binominal distribution probabilities, and the details are provided in Table 3-4 and Table 3-5. For example, if the true RR=20% for trametinib and dabrafenib combination, the probability of observing < 6 responses out of 20 LGG subjects (observed response rate < 30%) is approximately 80%, and the probability of observing < 3 responses out of 10 LCH subjects (observed response rate < 30%) is approximately 68%. If the true RR=50%, the probability of observing at least 6 responses is > 97% given 20 LGG subjects, and the probability of observing at least 3 responses is > 94% given 10 LCH subjects. Table 3-6 provides the corresponding 95% CIs around potential observed objective response rates given N=20 subjects. The corresponding 95% CIs for potential observed response rates given N=10 is shown in 3.

Table 3-4 Exact Binomial Probabilities of Observing less than 6 and at least 6 Responses in 20 Subjects

True RR	Probability of Observing < 6 responses in 20 Subjects	Probability of Observing ≥ 6 Responses in 20 Subjects
20%	0.80	0.20
25%	0.62	0.38
30%	0.42	0.58
35%	0.25	0.75
40%	0.13	0.87
45%	0.06	0.94
50%	0.02	0.98
55%	0.01	0.99

Table 3-5 Exact Binomial Probabilities of Observing less than 3 and at least 3 Responses in 10 Subjects

True RR	Probability of Observing < 3 responses in 10 Subjects	Probability of Observing ≥ 3 Responses in 10 Subjects
20%	0.68	0.32
25%	0.53	0.47
30%	0.38	0.62
35%	0.26	0.74
40%	0.17	0.83
45%	0.10	0.90
50%	0.05	0.95
55%	0.03	0.97

Table 3-6 Exact Binomial 95% Confidence Intervals around Potential Observed Objective Responses Rates for 20 Subjects

Observed Objective Response Rate	Exact 95% Confidence Interval (%) (N=20)
20%	5.7, 43.7
30%	11.9, 54.3
40%	19.1, 63.9
50%	27.2, 72.8
60%	36.1, 80.9
70%	45.7, 88.1
80%	56.3, 94.3

4 Change to protocol specified analyses

No changes from the protocol specified analyses were made.

5 Appendix

5.1 Imputation rules

In general, imputed partial dates will not be used to derive study day, duration (e.g. duration of adverse events), or elapsed time variables.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition partial dates may be imputed for 'slotting' data to study time periods (see [Section 9.3 in Protocol]) or for specific analysis purposes as outlined below.

5.1.1 Study drug

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

Scenario 1: If the dose end date is completely missing and there is no Study Treatment Discontinuation 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 dose end date is completely or partially missing and the Study Treatment Discontinuation page is available:

Case 1: The dose end date is completely missing, and the Study Treatment Discontinuation 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 Study Treatment Discontinuation date:

Use Dec31yyyy

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

Use Study Treatment Discontinuation date

Case 4: Both Year (yyyy) and Month (mm) are available for dose end date, and yyyy = the year of Study Treatment Discontinuation date and mm < the month of Study Treatment Discontinuation 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 treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date 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 o 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*

Missing Element	**Rule** (*=last treatment date plus 30 days (not death date, cut-off date, withdrawal of consent date))
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.

5.1.3 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.

5.1.4 Age calculation in Lab data

Following algorithm will be applied to derive the age at each visit in the Lab dataset and will be used in mapping the Lab normal reference ranges per age.

Step 1

For screening visit:
Use the age that the site provided in raw data (Age in Days, Age in Months, Age in Years)
Age in month will be age in days/30.4375.
Age in month will floor to integer, for example, if the calculated age in month is 14.3 then the age will be considered as 14 months and will be used when mapping with local reference ranges.

For other visits:
If Age is provided in Days, Age at each visit calculated as [Date of sample Collection(LBDT) - ICF date + Age in Days]
If Age is provided in Months, Age at each visit is calculated as [Date of sample Collection(LBDT) - ICF date + Age in Months + 15 days]
If Age is provided in Years, , Age at each visit is calculated as [Date of sample Collection(LBDT) - ICF date + Age in Years + 6 months].
If age is missing in demo then age in each visit is calculated as [Date of sample Collection(LBDT) - ICF date.
Age in month will be age in days/30.4375.

Step 2
If reference ranges are not mapped and still missing from Step 1, apply the following rules. If Age is provided in Days, Age at each visit = [Date of sample Collection(LBDT) - ICF date + Age in Days]
If Age is provided in months, Age is [Date of sample Collection(LBDT) - ICF date + Age in Months - 15 days] <=Age at each visit < [Date of sample Collection(LBDT) - ICF date + Age in Months + 15 days]
If Age is provided in years, Age is [Date of sample Collection(LBDT) - ICF date + Age in Months – 6months] <= Age at each visit < [Date of sample Collection(LBDT) - ICF date + Age in Months + 6months]

For both cases above, when there are more than one age ranges, select the ranges in order of (1) lower range (2) upper range. For example, if the age ranges are 13-60 and 61-119, then choose 13-60.

5.2 AEs coding/grading

Adverse events (AEs) will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

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). The CTCAE grade of 5 (death) is not used; rather, ‘fatal’ is collected as AE outcome and death information is also collected on a separate (e)CRF page.

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 4.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

For laboratory tests where grades are not defined by CTCAE v4.0, results will be graded by the low/normal/high 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.

Lab normal reference ranges

Local laboratory reference ranges will be collected throughout the study and will be provided by derived age at each visit using the age calculation algorithm provided in Appendix 5.14.

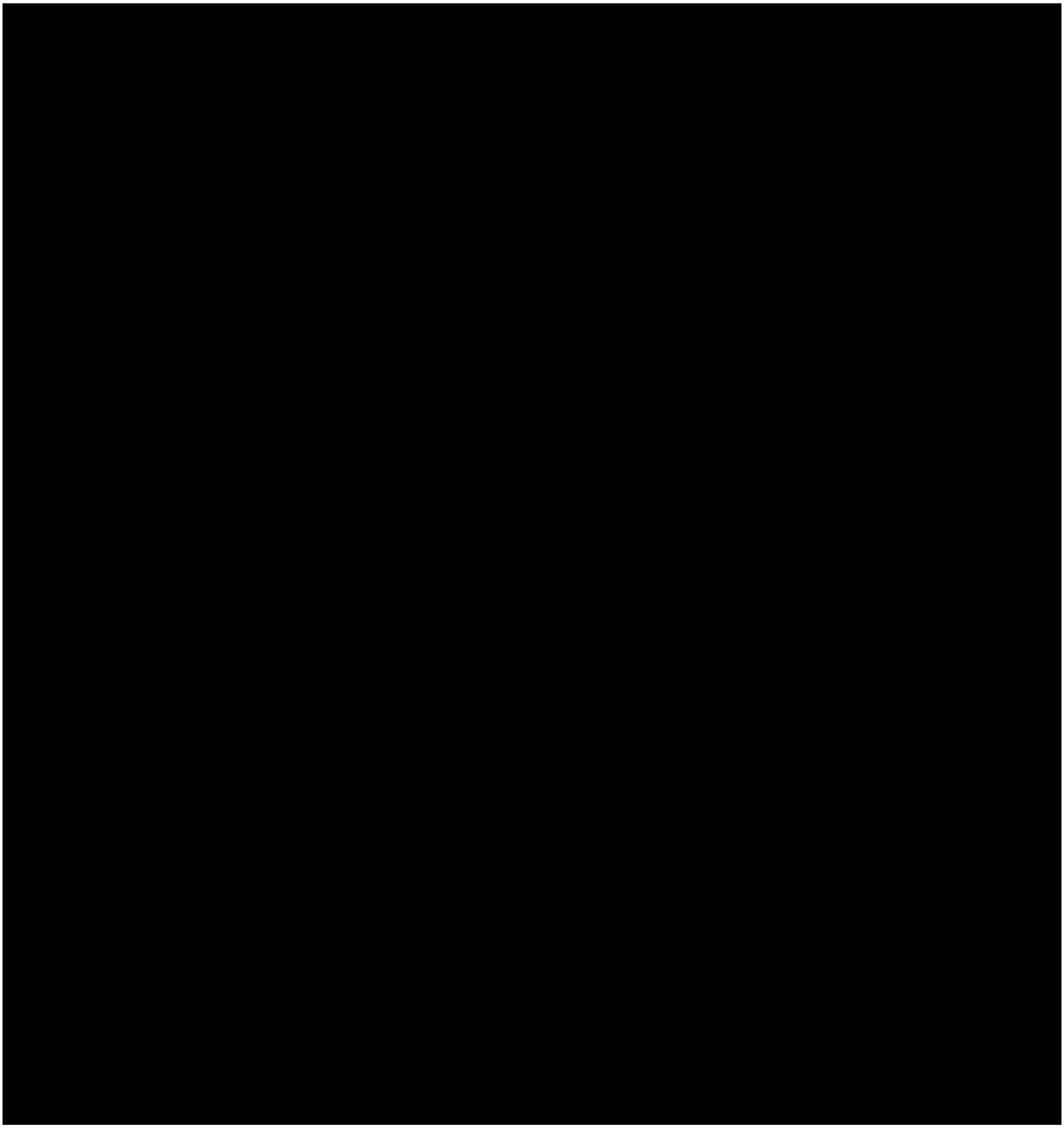
5.4 Statistical models

5.4.1 Primary analysis

For Part A, Part B, Part C, and Part D there are no formal statistical hypothesis are to be tested. As stated in protocol, the primary focus of the study is to characterize the safety and tolerability of trametinib and to determine the safe and tolerable dose.

5.4.2 Key secondary analysis

There is no key secondary objective.



[redacted]

6 Reference

1. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
2. Mercedes de Onis et al (2007). Development of a WHO growth reference for school-aged children and adolescents. Bulletin of the World Health Organization, 85, 660-667.

[redacted]