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Clinical Development

Dabrafenib+Trametinib®

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Protocol 200104: An Open-Label, Multi-Center Study to Investigate the Objective Response Rate of Dabrafenib in Combination with Trametinib in Subjects with BRAF V600 Mutation-Positive Melanoma

Statistical Analysis Plan (SAP)

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06-Apr-2018	Prior to DB lock	Creation of amendment 1 • Addition of PK samples for subjects with Day 1 or Day 15 samples • Revision of secondary objectives and endpoints in relation with the updated PK schedule • Update the RAP in line with Novartis RAP template	Second version	2.9 2.10

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CR	Complete Response
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DOR	Duration of Response
eCRF	Electronic Case Report Form
EOT	End of Treatment
FAS	Full Analysis Set
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCI	National Cancer Institute
o.d.	Once Daily
ORR	Objective Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Progression Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study 200104 (DRB436B2205), a phase II, open label, multi-center study to investigate the objective response rate of Dabrafenib in combination with Trametinib in subjects with BRAF V600 mutation-positive melanoma.

The content of this SAP is based on protocol DRB436B2205 Amendment v04. All decisions regarding primary analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1. Study design

This is a single-arm Phase II , open-label, multi-center study evaluating safety and efficacy of dabrafenib and trametinib combination therapy in BRAF V600 mutant-positive melanoma.

Approximately 65 subjects will be enrolled in the study.

Overall response rate (ORR), as assessed by local investigators review of tumor response and using RECIST 1.1 criteria, is the primary endpoint in this study.

The primary analysis will be performed after all subjects have been followed for at least 16 weeks or have at least 2 tumor assessments or have discontinued study.

Treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent, or study completion. After treatment discontinuation, subjects will be followed for survival and disease progression as applicable.

Survival and new anti-cancer therapy follow-up will continue until study completion. The study completion is defined as:

- In case all subjects stop study treatment within 48 weeks after Last Subject First Visit(LSFV): the study is completed once the last subject has completed the 48 weeks survival follow-up or all subjects die or loss to follow-up, whichever comes first.
- In case some subjects are still on study treatment 48 weeks after LSFV: the study is completed once all subjects stop study medication, or all subjects who are still on study medication can have access to alternative supply of MEK/BRAF inhibitors, whichever comes first.

Doses of study treatment may be modified and/or interrupted for management of toxicities associated with study treatment.

No formal interim efficacy analysis is planned for this study.

1.2. Study objectives and endpoints

Table 1.1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the objective response rate (ORR) of dabrafenib in combination with trametinib in subjects with BRAF V600 mutation-positive, unresectable or metastatic acral lentiginous or cutaneous melanoma	• ORR is defined as the percentage of subjects with evidence of a confirmed complete response (CR) or partial response (PR) as per RECIST v1.1 [Eisenhauer, 2009].
Secondary	
• To further evaluate the antitumor activity (progression-free survival (PFS), duration of response (DOR), and overall survival (OS)	• PFS is defined as the time from first dose of study treatment until the first date of either objective disease progression or death due to any cause. • Duration of response is defined as the time from first documented evidence of CR or PR until the earliest date of documented radiological progression or death due to any cause among subjects who achieved a confirmed CR or PR. • OS is defined as the interval from first dose of study treatment to the date of death, irrespective of the cause of death; subjects still alive will be censored at the date of the last contact.

Objectives	Endpoints
• To assess exposures to dabrafenib, dabrafenib metabolites, and trametinib after a single dose and at steady-state, and characterize the population pharmacokinetics and pharmacodynamics of dabrafenib and trametinib	• Trametinib, dabrafenib and dabrafenib metabolites concentrations by visit. For Mainland Chinese subjects with day 1 or day 15 samples， noncompartmental PK parameters include trametinib, dabrafenib and dabrafenib metabolites Cmax, tmax, Cτ, AUC(0-t), and AUC(0-8); AUC(0-12) (dabrafenib and dabrafenib metabolites only), AUC (0-24) (trametinib only) and the dabrafenib metabolite to dabrafenib ratio of AUC(0-t), the accumulation ratio calculating by using the pharmacokinetic parameters from Day 1 or Day 15 need to be provided. Population PK parameters include, apparent clearance following oral dosing (CL/F), volume of distribution (V/F), and absorption rate constant (Ka) for dabrafenib and trametinib.
• To evaluate the safety and tolerability of dabrafenib and trametinib	• Safety as measured by clinical assessments including vital signs and physical examinations, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), eye exams, chemistry and hematology laboratory values, and adverse events (AEs).
[redacted]	

Objectives	Endpoints
[redacted]	

2. Statistical methods

2.1. Data analysis general information

SAS version 9.3 software will be used to perform all data analyses and to generate tables, figures and listings.

Data will be summarized following Novartis outputs shells, however data model will follow GSK legacy data (IDSL).

Data included in the analysis

The analysis cut-off date for the primary analysis of study data will be established after all enrolled subjects have completed at least 16 weeks of treatment or have at least 2 tumor assessments or have discontinued study. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as ‘ongoing. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

The analysis cutoff date for the final analysis of study data will be established after the study completion (See section 1.1 for the definition of study completion).

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of subjects enrolled at centers, no center effect will be assessed.
Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by Mainland Chinese and all subjects; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by Mainland Chinese and all subjects.

Mainland Chinese population means the subjects enrolled from mainland China. All subjects means all subjects enrolled to the study.

2.1.1. General definitions

2.1.1.1. Study drug and study treatment

Study drug and study treatment both refer to Dabrafenib in Combination with Trametinib.

2.1.1.2. Date of first/last administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug is administered and recorded on the exposure form. For the sake of simplicity, the date of first administration of study drug will also be referred as start date of study drug.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug is administered and recorded on the exposure form. This date is also referred as last date of study drug.

2.1.1.3. Study day

The study day for all assessments (e.g. tumor assessment, death, disease progression, tumor response, performance status, adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption) will be calculated using the start date of study drug as the origin. For assessments occurring after or on the start date of study drug, study day will be calculated as:

Study Day =Event date - start date of study drug + 1.

The first day of study drug is therefore study day 1.

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) occurring prior to the start of the study drug, study day will be negative and will be calculated as:

Study Day = Event date - start date of study drug.

The study day will be displayed in the data listings.

2.1.1.4. 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.

2.1.1.5. Baseline

Baseline will be defined as the most recent non-missing value prior to the first dose of study treatment. For laboratory data, baseline will be defined as the most recent non-missing value from a laboratory prior to the first dose of study treatment.

If subjects have no value as defined above, the baseline results will be considered missing.

2.1.1.6. On-treatment assessment/event and observation periods

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

1. ***pre-treatment period***: from day of subject'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.

2.1.1.7. Last contact date

The last contact date will be derived for subjects not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Last contact date/last date subject was known to be alive from Survival Follow-up page	Subject status is reported to be alive
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.

Source data	Conditions
Tumor (RECIST) assessment date	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date . The cut-off date will not be used for last contact date, unless the subject was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

The last contact date will be used for censoring of subjects in the analysis of overall survival.

2.2. Analysis sets

2.2.1. Analysis Populations

Full Analysis Set

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

Safety

The **Safety Set** includes all subjects who received any study treatment (i.e. at least one dose of any component of the study treatment). Subjects will be analyzed according to the study treatment actually received.

- The actual treatment received corresponds to the assigned treatment if subjects took at least one dose of that treatment.

Pharmacokinetic analysis set (PAS)

The Pharmacokinetic Analysis Set (PAS) includes mainland Chinese subjects who provide an evaluable PK profile on Day 1 or Day 15 and without any dose interruption, reduction or overdosing. A profile is considered evaluable if all of the following conditions are satisfied.

- Subject receives the treatment dose of both dabrafenib and trametinib on the profile day.

- Subject provides at least one primary PK parameter of both dabrafenib and trametinib.

2.2.2. Withdrawal of Informed Consent

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

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

Additional data for which there is a separate informed consent, e.g. PK, [redacted] etc., collected in the clinical database without having obtained that consent will not be included in the analysis.

2.2.3. Subgroup of interest

Not applicable

2.3. Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by mainland Chinese and all subjects. Categorical data (e.g. sex, age groups: <65 and ≥65 years, country of origin, race, ethnicity, ECOG performance status, smoking history) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age, weight, height, and Body Mass Index (BMI)) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). Height is collected only once in the study. Baseline weight is the last non-missing value observed before the first administration of study drug. BMI will be calculated using height and baseline weight:

$$\text{BMI } (kg/m^2) = \text{weight } [kg] / (\text{height } [m])^2$$

Diagnosis and extent of cancer

Summary statistics will be tabulated for disease history.

2.3.1. Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e)CRF will be summarized and listed. Separate summaries will be presented for ongoing (current) and historical (past) medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT) by mainland Chinese and all subjects. Medical history and current medical conditions are coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.
Medical history and characteristics (e.g., time since initial diagnosis, stage at initial diagnosis, etc.), tobacco use, alcohol intake and family cardiac and cancer (eg: melanoma related) history will be summarized and listed.

Other

All data collected at baseline including source of child bearing potential [redacted] informed consent, treatment beyond progression informed consent, and optional tumor biopsy informed consent will be listed.

2.3.2. Patient disposition

Enrollment by country and center will be summarized for all subjects using the FAS. The number (%) of treated subjects included in the FAS will be presented. The number (%) of subjects in the FAS who are still on treatment, who discontinued the study and the reason for discontinuation will be presented by mainland Chinese and all subjects.

The following summaries will be provided (with % based on the total number of FAS subjects):

- Number (%) of subjects who are still on-treatment (based on the both dabrafenib and trametinib 'Study Treatment Discontinuation' pages not completed);
- Number (%) of subjects who discontinued the study treatment phase (based on both dabrafenib and trametinib 'Study Treatment Discontinuation' pages)
- Primary reason for study treatment phase discontinuation (based on dabrafenib or trametinib 'Study Treatment Discontinuation' pages)

2.3.3. Protocol deviations

The number (%) of subjects in the FAS with important protocol deviation will be tabulated by deviation category (as specified in the Protocol Deviation Management Plan) overall for the FAS. Major protocol deviations leading to exclusion from analysis sets will be tabulated separately by Mainland Chinese and all subjects. All the important protocol deviations including the description will be listed.

Analysis sets

The number (%) of subjects in each analysis set (defined in Section 2.2.1) will be summarized.

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

2.4.1. Study treatment / compliance

Extent of exposure to dabrafenib and trametinib will be summarized separately.

The duration of exposure to study treatment in months (from first day to last day of treatment) will be summarized. Descriptive statistics including mean, median, standard deviation, minimum, and maximum will be calculated for duration of exposure to study treatment. Moreover, duration of exposure to study treatment will be categorized in different time period: < 3 months, 3 months to 6 months, >6 months to 12 months, >12 months to 24 months, >24 months to 36 months and >36 months.

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 dates of exposure to investigational drug.

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

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

For subjects who did not take any drug the cumulative dose is by definition equal to zero.

The subject daily dose, defined as the cumulative dose divided by the duration of exposure for each subject, and the cumulative doses will be summarized.

Duration of exposure by person time will be summarized by trametinib, dabrafenib and combination treatment. Summary will also be produced by age group and gender. Person time of a specified group is defined as the total exposure time experienced by all subjects belonging to that specified group.

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

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

Dose intensity and relative dose intensity

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

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

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

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

Planned dose intensity (PDI) is defined as follows:

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

Relative dose intensity (RDI) is defined as follows:

RDI = DI (dosing unit / day) / PDI (dosing unit / day).

DI and RDI will be summarized for each of the study treatment components.

The following tables provide the examples for the calculations, however, the final numbers should be based on the acture data, not from the following tables.

Table 2-2 Examples of dabrafenib dose administration and exposure

DAR record number	Start/End Date	Dose Prescribed (mg), frequency	Dose Administered (mg) [total daily]	Dose Changes, Dose Interruption	Dose Permanently Discontinued	Reason
1	01Jan2016 / 05Jan2016	150 mg BID	300	No	No	
2	06Jan2016 / 03Feb2016	150 mg BID	200	Yes	No	AE
3	04Feb2016 / 25Feb2016	150 mg BID	300	No	No	

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

Planned cumulative dose (for 56 days) = 300*56 days = 16800 mg

Actual cumulative dose = 300*5 + 200*29 + 300*22 = 13900 mg

Dose intensity = 13900 mg / 56 days = 248.21 mg/day

Planned dose intensity = 16800 mg / 56 days = 300 mg/day

Relative dose intensity = DI / PDI = (248.21 mg/day) / (300 mg/day) = 0.83

Table 2-3 Examples of trametinib dose administration and exposure

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

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

Planned cumulative dose (for 56 days) = 2*56 days = 112 mg

Actual cumulative dose = 2*10 + 0*5 + 1*41 = 61 mg

Dose intensity = 61 mg / 56 days = 1.09 mg/day

Planned dose intensity = 112 mg / 56 days = 2 mg/day

Relative dose intensity = DI / PDI = (1.09 mg/day) / (2 mg/day) = 0.54

Dose reductions, interruptions or permanent discontinuations

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

'Dose interrupted', and 'Dose permanently discontinued' fields from the Study Treatment CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

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

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

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

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated

dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

A listing of planned and actual treatments will be produced.

A summary of overall compliance for trametinib and dabrafenib based on the exposure data will be producedseparately. Percentage overall compliance will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, percentage overall compliance will be categorized and summarized by < 80%, 80%-105%, and >105%.

The calculation of overall compliance is based on the entire interval of dosing for each of the drug. The formula for daily dose medication is compliance (%) = [total cumulative actual dose / (duration of study treatment * prescribed dose)]*100 where duration of study treatment is last dose-first dose +1.

The formula for overall compliance for dabrafenib is:
Compliance (%) = [total cumulative actual dose / (duration of study treatment * prescribed dose per day)]*100,
where duration of study treatment = last dose-first dose +1.

The formula for compliance for trametinib is:
Compliance (%) = [total cumulative actual dose / (duration of study treatment * prescribed dose per day)]*100,
where duration of study treatment = last dose-first dose +1.

A listing of overall compliance will be produced.

In addition, summaries of study treatment exposure and dose modifications (e.g. number of dose reductions, number of dose interruptions) will further characterize compliance. These analyses are described in Section 2.4.1

2.4.2. Prior, concomitant and post therapies

2.4.2.1. Prior anti-cancer therapy

The number and percentage of subjects who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy, immunotherapy etc.), setting (e.g. adjuvant, metastatic, etc.) and also by lowest ATC class, preferred term and treatment. Summaries will include total number of regimens, best response and time from last treatment to progression for the last therapy. The

medication therapy type of any combination therapy will be classified based on the following order: immunotherapy, chemotherapy, biologic therapy (other than immunotherapy), small molecular targeted therapy, hormonal therapy, radioactive therapy. For example, a combination therapy of chemotherapy and immunotherapy will be classified as 'immunotherapy'.For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Prior systemic anti-cancer therapy (CTX) will be coded using GSK Drug coding dictionary, then summarized by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between ATC Level 1, Ingredient, and verbatim text. Prior anti-cancer surgery (MEDSX) and radiotherapy (RADIO) will be listed.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall and by means of frequency counts and percentages using FAS.

2.4.2.2. Concomitant medications

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

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

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

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

A summary of prophylactic treatment and listing of prophylactic medications for the treatment of rash, pyrexia and diarrhea will be produced.

2.5. Analysis of the primary objective

The primary objective is to demonstrate the antitumor activity of Dabrafenib in combination with trametinib as measured by ORR in subjects with BRAF V600 mutation-positive melanoma.

2.5.1. Primary endpoint

The primary end point, ORR is defined as the percentage of subjects, who have a confirmed complete response or a partial response based on RECIST 1.1[Eisenhauer, 2009] and are evaluated by the investigtor, among all subjects who have been enrolled and received at least one dose of investigational product. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of overall response. Confirmation assessments must be performed no less than four weeks (28 days) after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required.

ORR is defined as the proportion of subjects with confirm response of complete response (CR) or partial response (PR) according to RECIST 1.1. ORR will be calculated based on the FAS using local investigators review of tumor assessment data. Subjects with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if a complete response was observed.

2.5.2. Statistical hypothesis, model, and method of analysis

The study will pursue an estimation strategy rather than formal hypothesis testing. This is reasonable given the proven performance of the combination therapy and the desire to estimate the effect in the Asian population. Since estimation is the goal, there are no formal hypotheses to be tested. 95% confidence limits for objective response rate (ORR) will be calculated. The minimal effect to be excluded from the lower end of the confidence interval for ORR will be 25%.

The primary objective will be supported by the calculation of objective response rate using the FAS population. The final analysis of ORR will be performed after all enrolled subjects have completed 16 weeks of treatment or have at least 2 tumor assessments or have otherwise discontinued study treatment.

The primary efficacy analysis ORR will be summarized using descriptive statistics (N,%) along with 2-sided exact 95% confidence interval (CI) [Clopper and Pearson 1934].

2.5.3. Handling of missing values/censoring/discontinuations

Subjects with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the percentage. No imputation will be performed for missing lesion assessments or tumor response data.

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

2.5.4. Supportive analyses

Not applicable

2.6. Analysis of the key secondary objective

There is no key secondary objective in this study.

2.7. Analysis of secondary efficacy objective(s)

The other secondary efficacy objectives are to describe PFS, OS, and DOR.

2.7.1. Secondary endpoints

Progression-Free Survival(PFS)

PFS is defined as the time from the date of the first dose to the date of the first documented progression or death due to any cause. PFS will be based on local investigators review of tumor assessments and using RECIST 1.1 criteria. The analysis will be based on FAS and will include all data observed up-to the cut-off date.

In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date or before the start of the new anticancer therapy date or loss to follow up, whichever is earlier. (See Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment). Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression for the primary analysis.

Overall Survival (OS)

Overall Survival (OS) is defined as the time from date of first dose to date of death due to any cause. A cut-off date will be established for each analysis of OS. All deaths occurring on or before the cut-off date in the FAS will be used in the OS analysis.

If a subject is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact (See Section 2.1.1.7 for additional details). The survival distribution of OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians intervals.

Duration of Response

Duration of response (DOR) only applies to subjects whose confirm overall response is complete response (CR) or partial response (PR) according to RECIST 1.1 based on local investigators review of tumor assessment data. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death. Subjects continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment using the censoring rule described for PFS analysis (See Section 2.7.3 for additional details).

2.7.2. Statistical hypothesis, model, and method of analysis

Similar to the analysis of primary endpoint, there is no formal hypothesis testing. PFS, OS and DOR will be summarized descriptively using Kaplan-Meier medians and quartiles.

Since there is a single primary endpoint (ORR), supported by secondary endpoints, the nominal level of significance for the primary analysis will not be affected by multiplicity.

PFS based on local investigators review of tumor assessments and using RECIST 1.1 criteria is a secondary endpoint in this trial and will be analyzed using the same conventions as that of the primary efficacy analysis. The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented.

The survival distribution of OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals[Brookmeyer and Crowley 1982] of the medians intervals.

DOR will be listed and summarized for all subjects in the FAS with confirmed CR or PR. The distribution of duration of response will be estimated using the Kaplan-Meier method and the median duration of response will be presented along with 95% confidence interval only if a sufficient number of responses is observed.

2.7.3. Handling of missing values/censoring/discontinuations

For subjects who have not progressed or died at the time of the PFS or DOR analysis, censoring will be performed using the rules described in table 2-4 or first dose for subjects without any adequate post baseline assessments.

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

If there is no adequate baseline assessment, the subject will be censored at their date of the first dose. Subjects without any adequate post baseline tumor assessments will be censored at the date of the first dose. Subjects who progressed or died after an extended period without adequate assessment will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate assessment is defined as an assessment where the investigator determined response is CR, PR, or SD. The date of response at that assessment will be used for censoring. As the assessment schedule changes through the course of the protocol (i.e. every 8 weeks until week 56 and then every 12 weeks thereafter), the following rules will be used for identifying extended loss to follow up or extended time without an adequate assessment(i.e. two or more missed assessments) .

- If death or PD is on or prior to day 399 (week 56 + 7 day window), then a subject will be identified as an extended loss to follow up if the subject did not have an adequate assessment during the time period of 119 days (16 weeks + 7 day window) prior to death or PD;
- Else if death or PD is after day 399 (week 56 + 7 day window) and prior to day 567 (week 80 + 7 day window), then a subject will be identified as an extended loss to follow up if the subject did not have an adequate assessment during the time period of 147 days (8 weeks + 12 weeks + 7 day window) prior to death or PD.
- Else if death or PD is after day 567 (week 80 + 7 day window), then a subject will be identified as an extended loss to follow up if the subject did not have an adequate assessment during the time period of 175 days (24 weeks + 7 day window) prior to death or PD.

For subjects who receive subsequent anti-cancer therapy the following rules will apply:

- If the start date of the anti-cancer therapy is partial (i.e. either missing the day but has the month and year available or missing both day and month), the imputation rules described in Section 5.1 will be applied. No imputation will be made for completely missing dates.

- If anti-cancer therapy is started without documented disease progression or is started prior to documented disease progression, then PFS will be censored at the date of the last adequate assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy the assessment will be used - as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy). The date of response at the last adequate assessment will be used as the censoring date.
- If a subject has only a baseline visit or does not have an adequate assessment that is no later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of the first dose.

Refer to Table 2-4 for censoring and event date options and outcomes for PFS.

Table 2-4 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of the first dose	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Date of last adequate assessment on or prior to starting new anti-cancer therapy (or crossover treatment)	Censored
Death before first PD assessment (including death at baseline or prior to any adequate assessments)	Date of death	Progressed

Overall survival (OS)

If a subject is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date subject was alive, i.e., last contact date (see Table 2-1).

2.8. Safety analyses

All safety analyses will be based on the safety set.

2.8.1. Adverse events (AEs)

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose reductions, AEs leading to dose interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced.

A summary of non-serious AEs that occurred in strictly 10% of the subjects or above will be provided (no rounding for the percentage will be used in terms of 10% threshold, e.g. event with 9.9% incidence rate should not be included in this table). The summary will be displayed by SOC and PT. (for clinicaltrials.gov purpose)

AEs will be graded according to the CTCAE v4.0. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Activities (MedDRA dictionary) (MedDRA 20.1).

The relationship between MedDRA SOC, PT, and Verbatim Text will be displayed.

A summary of number and percentage of subjects with any AE by maximum grade will be produced. AEs will be sorted by Preferred term (PT) in descending order of incidence. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order of incidence by PT only and 2) in descending order of incidence by System Organ Classes (SOC) and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

A separate summary will be provided for study treatment-related AEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as “Yes”. A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as ‘Yes’ or missing. The summary table will be displayed in descending order of incidence by PT only.

All AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for study treatment-related SAEs and fatal SAEs. The summary tables will be displayed in descending order of incidence by PT only.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for

- Fatal SAEs
- Non-Fatal SAEs

The following summaries will be provided for EudraCT purpose:

- Serious adverse events occurrence, regardless of study drug relationship, by primary SOC and PT
- Non-serious adverse events occurrence, regardless of study drug relationship, by primary SOC and PT
- Serious adverse events occurrence, with suspected study drug relationship, by primary SOC and PT

One occurrence is counted if AEs match at SOC & PT and have relationsh

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

AEs will be summarized by number and percentage of subjects 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 subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject 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; overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE, any dose reductions/interruptions etc use OSO shell), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to

treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy, and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term). 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.

If the same subject has more than one AE (irrespective of study treatment causality, seriousness and severity) 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 legal requirements of clinicaltrials.gov and EudraCT, two required tables for on-treatment adverse events which are not SAE's with an incidence greater than and equal to 5% and on-treatment SAE's and SAE's suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

2.8.1.1. Adverse events of special interest / grouping of AEs

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of events.

The events of special interest will be analysed using the most updated asset specific AESI (Adeverse Event of Special Interest) at the time of analaysis.

Summaries of the number and percentage of subjects with these events will be provided for each type of events separately upon the real incidence of the events if data permits. The summary of event characteristics will also be provided, including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, the outcome of the event, maximum grade and the action taken for the event. The worst case approach will be applied at subject level for the event outcome, maximum grade and the action taken, i.e. a subject will only be counted once as the worst case from all the events that subject had. In addition, onset and duration of the first occurrences for each type of events will be summarized.

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

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to dabrafenib and trametinib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA

queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on treatment period will be summarized.
Summaries of these AESIs will be provided, (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 subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process.

All deaths occurring any time from the time of informed consent to the clinical cut-off date will be summarized based on the number and percentage of subjects. This summary will classify subjects by time of death relative to the last dose of medication (> 30 days or ≤ 30 days) and primary cause of death (disease under study, SAE related to study treatment, or other). A supportive listing will be generated to provide subject-specific details on subjects who died.

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced, system organ class and preferred term.

All deaths and deaths prior to starting treatment will be listed.

2.8.3. Laboratory data

The assessment of laboratory toxicities will examine the following laboratory tests:

Hematology: Hemoglobin (HGB), White Blood Cell (WBC) count, Total Neutrophils, Lymphocyte, Monocyte, Basophil and Eosinophil counts, and Platelet count. Basophils, Eosinophils and Monocytes are not gradable by CTCAE v4.0.

Clinical Chemistry: Sodium, Potassium, Calcium, Glucose, Blood Urea Nitrogen (BUN), Creatinine, Estimated Creatinine Clearance, Albumin, Lactate Dehydrogenase (LDH), and phosphate. BUN, LDH and Estimated Creatinine Clearance are not gradable by CTCAE v4.0. For Sodium, Potassium, Calcium, Phosphate, Lymphocyte and Glucose two bi-directional parameters (hyper and hypo), the tests will be graded by CTCAE v4.0 in both directions.

Liver Function Tests: Aspartate amino transferase (AST), Alanine amino transferase (ALT), Alkaline phosphatase, Total bilirubin (total) and Direct bilirubin. All these tests are gradable by CTCAE v4.0.

Coagulation Tests: Prothrombin time (PT) or International Normalized Ratio (INR), and partial thromboplastin time (PTT). These tests are collected only at baseline. Therefore these tests will not appear in any summaries of changes from baseline.

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum on-therapy grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. In addition, the summary will include grade increase from baseline by scheduled visits. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v4.0, summaries of worst case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized at each scheduled visit as well as for the worst case post baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories. Flag the earliest worst-case normal range values per time point. The worst-case for normal range values is bi-directional (either High or Low or both). If subject has both High and Low values in same time point, then flag both the earliest High record and the earliest Low record. If subject does not have a High or a Low value during the time point, then flag the subject's earliest in-range value. For visit timepoints: Baseline records are always flagged. Pre-therapy records, imputed records, and unscheduled records are not eligible for flagging.

Separate summary tables for (hematology, chemistry, liver function and coagulation) laboratory tests will be produced.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit. For subjects with a history of chronic Hepatitis B and/or Hepatitis C, the following tests will be performed at Screening:

- Viral hepatitis serology (HBs Antigen, HBc Antibody, HBs Antibody, HCV Antibody);
- Hepatitis BDNA; and/or
- Hepatitis C RNA.

As it is anticipated that the number of subjects with a history of chronic Hepatitis B and/or Hepatitis C will be small these data will only be listed and not summarized.

Summaries of hepatobiliary laboratory events including possible hy's law cases will be provided in addition to what has been described above.

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.

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

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

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

Liver function parameters

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

The following summaries will be produced:

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

ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

Potential Hy's Law events are defined as those subjects with concurrent occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-treatment period. Further medical review has to be conducted to assess potential confounding factor such as, liver metastates, liver function at baseline etc.

2.8.4. Other safety data

2.8.4.1. ECG and cardiac imaging data

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits.

The QT and QTcB values based on Bazett formula will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (≤450), Grade 1 (>450 and ≤480), Grade 2 (>480 and ≤500), and Grade 3 (>500). Summaries of grade increase will be provided. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 at each scheduled in the worst case post baseline only.

The changes in QT and QTcB values will be categorized into the clinical concern ranges which are specific to changes in QT and QTcB: (>30 and ≤60) and (> 60) msec. A summary of change in QTcB value will display the number and percentage of subjects with a change within each range at each scheduled assessment time and in the worst case post baseline. Worst case post baseline will include both scheduled and unscheduled visits. Subjects with missing baseline values will be excluded from this summary.

The summaries for the QTcB will use the collected value based on Bazett formula.
In addition, ECG interval values will be also be summarized.

Listings of abnormal ECG findings and a listing of ECG values will be provided.

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

- Any increase
- No change
- Any decrease
    - >0 - < 10 Decrease
    - 10 - 19 Decrease
    - >= 20 Decrease
- ≥10 decrease and ≥LLN
- ≥10 decrease and <LLN

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

LVEF results will also be listed with subject level details including absolute change from baseline.

Note: If there is any change in the methodology used throughout the study compared to baseline, the post-baseline values for which the methodology differs from baseline will be discarded in the tables presenting comparisons to baseline.

A listing of subjects with newly occurring clinically significant abnormality will be produced.

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.

Data analysis

12-lead ECGs including QT, QTcB, and RR intervals will be obtained local for each subject during the study. ECG data will be read and interpreted locally

The number and percentage of subjects with notable ECG values will be presented.

- QT, QTcF, or 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
- RR
  - value <600 ms
  - value >= 600 ms

A listing of all ECG assessments will be produced and notable values will be flagged. A separate listing of only the subjects with notable ECG values may also be produced. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.4.2. Vital signs

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

Data handling

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

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-5 below.

Table 2-5 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
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	

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

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

2.8.4.3. Ophthalmic Examination

Baseline data and data from week 4 will be summarized based on number and percentage of subjects who receive an ocular exam. As post baseline exams (except week 4) are only performed as clinically indicated, data beyond week 4 will only be listed.

2.8.4.4. Echocardiograms (ECHO)

Shift tables comparing baseline to worst post-baseline cardiac imaging (ECHO) overall interpretation will be provided.

Note: If there is any change in the methodology used throughout the study compared to baseline, the post-baseline values for which the methodology differs from baseline will be discarded in the tables presenting comparisons to baseline.

Descriptive statistics of the left ventricular ejection fraction (LVEF) at baseline, worst post-baseline value and change from baseline to worst post-baseline value will be provided.

2.8.4.5. ECOG performance status

The ECOG PS scale (Table 2-6 will be used to assess physical health of subjects, ranging from 0 (most active) to 5 (least active):

Table 2-6 ECOG Performance Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Shift tables of ECOG performance status at baseline to worst post-baseline ECOG status by score will be provided. Shift tables of ECOG performance status at baseline to best post-baseline ECOG status by score will also be provided. ECOG performance status at each time point will be listed.

2.8.4.6. Dermatological Exams

The results of dermatological exams will be included in tables (category of normal, abnormal-not clinically significant and abnormal-clinically significant) as well as in corresponding SAEs and summarized in SAE forms, if applicable.

2.9. Pharmacokinetic endpoints

Pharmacokinetic analysis for mainland Chinese patients with day 1 or day 15 samples will be the responsibility of the PK Sciences department within Novartis. Plasma dabrafenib and metabolites including hydroxy- , desmethyl-, and carboxy-dabrafenib and trametinib concentration-time data will be analyzed by standard noncompartmental methods in subjects from whom the full PK blood sample scheme were collected. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time

data, the following pharmacokinetic parameters will be determined for dabrafenib, dabrafenib metabolites and trametinib, as data permit:

For pharmacokinetic parameters on Day 1, Cmax, Tmax, AUC(0-t), AUC(0-8), AUCinf and apparent terminal phase half-life (T1/2) should be estimated for dabrafenib and dabrafenib metabolites. Cmax, Tmax, AUC(0-t) and AUC(0-8) should be estimated for trametinib. AUC(0-12) will be estimated for dabrafenib and metabolites only by using extrapolation method with half-life to predict the plasma concentration 12 hours after dosing. AUC(0-24) will be estimated for trametinib only. The dabrafenib metabolite to dabrafenib ratio of AUC(0-12) adjusted by molecular weight (Rm/p) also needs to be calculated.

For pharmacokinetic parameters on Day 15, Cmax, C_{trough}, Tmax, AUC(0-t) and AUC(0-8) should be estimated for trametinib, dabrafenib and dabrafenib metabolites. AUC(0-12) will be estimated for dabrafenib and metabolites only by setting the plasma concentration 12 hours after dosing equal to the predose concentration. AUC(0-24) will be calculated for trametinib only. The dabrafenib metabolite to dabrafenib ratio of AUC(0-12) adjusted by molecular weight (Rm/p) also needs to be calculated.

The accumulation ratio (Racc) will be calculated by using the pharmacokinetic parameters from Day 1 and Day 15 separately.

PK parameters

The PK parameters that will be determined are shown in Table 2-7

[redacted]

Table 2-7 Non-compartmental PK parameters for trametinib, dabrafenib and dabrafenib metabolites on Day 1 and Day 15 respectively

Cmax	The maximum (peak) observed plasma concentration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma concentration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time)
C_{trough}	Pre-dose (trough) concentration at the end of the dosing interval
$AUC(0-8)$	Area under the plasma concentration-time curve calculated from time zero (pre-dose) to 8h (mass x time x volume-1)

$AUC(0-12)$	Area under the plasma concentration-time curve calculated from time pre-dose to 12h (mass x time x volume-1)(dabrafenib and dabrafenib metabolites only)
$AUC(0-24)$	Area under the plasma concentration-time curve calculated from time zero (pre-dose) to 24h (mass x time x volume-1)(trametinib only)
$AUC(0-t)$	Area under the plasma concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUCinf	Area under the plasma concentration-time curve from time zero to infinity (mass x time x volume-1) on Day 1
Rm/p	The dabrafenib metabolite to dabrafenib ratio(AUC0-12,metabolites / AUC0-12,dabrafenib) adjusted by molecular weight
Racc	Accumulation ratio (AUC0-12,Day 15 / AUC0-12,Day 1) for dabrafenib and Accumulation ratio (AUC0-24,Day 15 / AUC0-24,Day 1) for trametinib

Descriptive statistics (n, arithmetic mean, standard deviation (SD), median, minimum and maximum, CV%, geometric mean, and geometric CV%) will be presented for all PK parameters defined in Table 2-7, where only n, median, minimum and maximum will be presented.

Coefficient of variation (CV) (%) is calculated as follows:

100*(SD/arithmetic mean).

Geometric CV (%) is calculated as follows:

sqrt (exp (variance for log transformed data)-1)*100.

All individual PK parameters for dabrafenib, dabrafenib metabolites and trametinib defined in Table 2-7 on day 1 and day 15 also will be listed respectively.

PK concentrations

Individual concentration-time profiles on day1 and day 15 for dabrafenib, dabrafenib metabolites and trametinib concentrations will be displayed graphically on the semi-log view respectively for PAS in mainland Chinese. In addition, the mean (+/- SD) concentration-time profiles for dabrafenib, dabrafenib metabolites and trametinib by treatment over time will be displayed graphically on the linear and semi-log view.

All individual plasma for dabrafenib, dabrafenib metabolites and trametinib concentration data will be listed by treatment for safety set.

Handling of PK data below LLOQ or missing

Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

Plasma concentration below the limit of quantitation (BLQ) values (1 ng/mL for dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib, 5 ng/mL for carboxy-dabrafenib and 0.250 ng/mL for trametinib) will be set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. BLQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and geometric CV%.

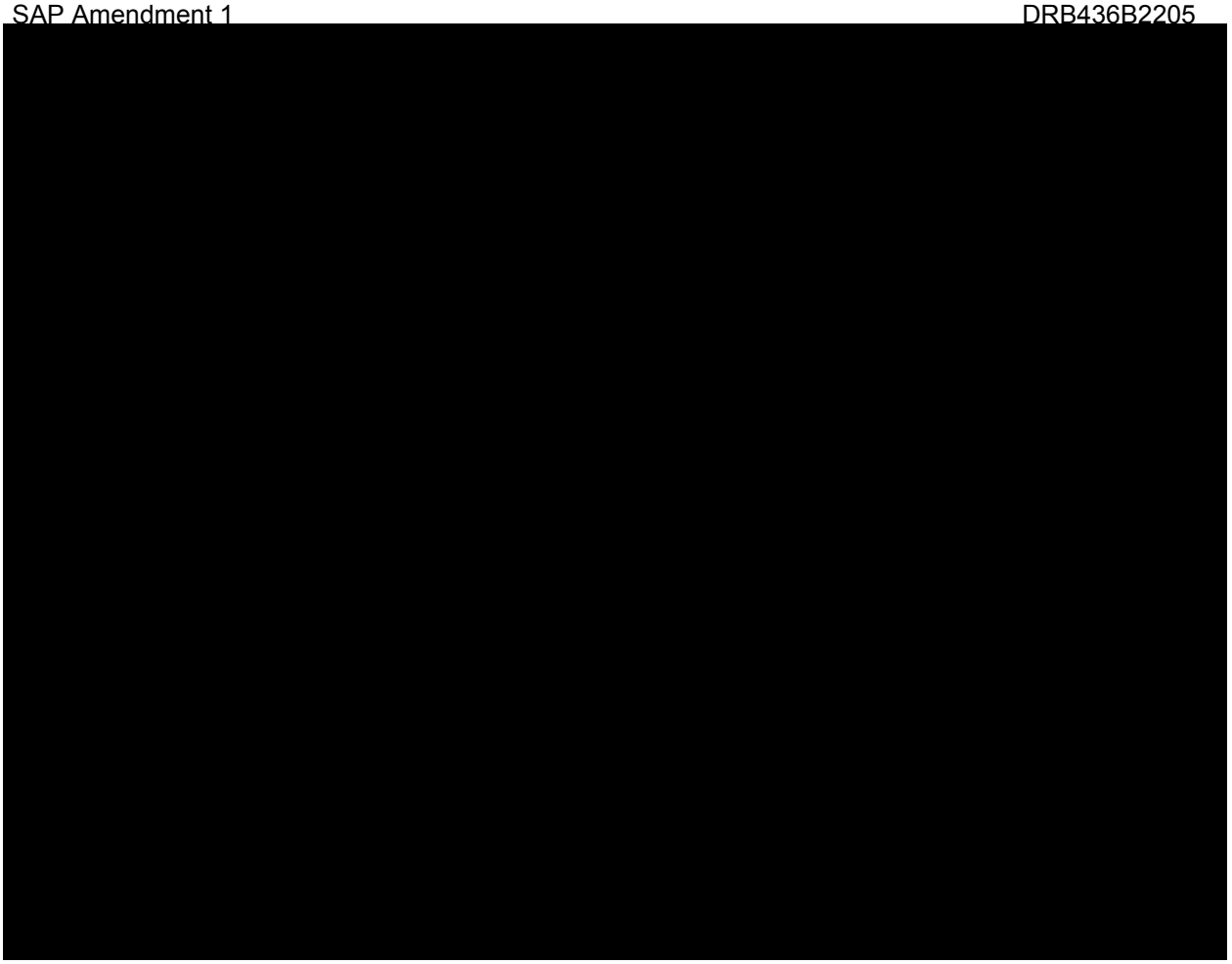
Population Pharmacokinetic Analysis

Mixed-effects pharmacokinetic models developed previously for dabrafenib and trametinib

2.10. PD and PK/PD analyses

2.11. Patient-reported outcomes

Not applicable.



2.14. Interim analysis

There is no interim analysis planned for this study.

3. Sample size calculation

3.1. Primary analysis

Approximately 65 subjects will be enrolled primarily based on clinical justification. This sample size was deemed to be sufficient to assess efficacy, safety and tolerability of Dabrafenib in combination with trametinib in Asian subjects with BRAF V600 Mutation-Positive Melanoma.

An exact binomial confidence interval will be calculated. Lower bound higher than 25% is considered to be clinically meaningful in this setting.

3.2. Power for analysis of key secondary variables

Not applicable.

4. Change to protocol specified analyses

Replace All Treated Subjects (ATS) to Full Analysis Set (FAS), and replace PK population to Pharmacokinetic Analysis Set (PAS).

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 relapse time variables. In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

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 EOT page and no death date, the subject is considered as on-going:

The subject should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

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

Use Dec31yyyy

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

Use EOT date

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

Use last day of the Month (mm)

Case 5: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm = the month of EOT date:

Use EOT date

For subject with missing exposure end dates at the time of data cutoff, the exposure end date will be imputed to the earliest of: the date of the data cutoff, the date of withdrawal from the study, or the death date.

The imputed exposure end date will be used to calculate cumulative dose and exposure duration. The imputed exposure end date will be stored in the exposure analysis dataset and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed. Imputed exposure end dates will also be stored on the study treatment end date variable.

For subjects who have missing end dates in their last exposure record because they are

still on study treatment, the on-therapy indicator variables (time in relation to study treatment) are assigned to on-therapy for all records where the 'dataset'.'date' is after or on the study treatment start date. Missing exposure end date imputation will be applied to both study treatments (dabrafenib and trametinib). The study treatment end date variable will hold the last date of exposure across both study treatments.

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

Subjects with missing start dates are to be considered missing for all study treatment component related calculations

5.1.2. AE, ConMeds and safety assessment date imputation

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

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

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

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

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

Missing Element	Rule (*=last treatment date plus 30 days provided it is not > (death date, cut-off date, withdrawl 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* • For post treatment period, no imputation will be done for completely missing dates
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period * • For post treatment period, set end date = earliest of 31DecYYYY or death date or cut-off date or withdrawl of consent date
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* • For post treatment period, set end date = earliest of last day of the month or death date or cut-off date or withdrawl of consent date
Date of progression from Prior anti-cancer therapy	• Only impute when a month and year are available but the day is missing. • Impute to last day of the month, also must be after the start date of therapy and prior to 'start of study treatment'. If 'start of study treatment ' is on the same month as prior therapy end date, then assign treatment start date minus one day for the prior therapy end date. • Use only for relevant exploratory efficacy analyses of time to progression from prior anti-cancer therapy regimens (i.e. not to be used for general radiotherapy or anti-cancer therapy summaries)

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.

5.2. AEs coding/grading

AEs will be graded according to the CTCAE v4.0. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Activities (MedDRA dictionary)(MedDRA 20.1).

5.3. Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

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

Imputation Rules

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

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

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

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

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

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

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

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

5.4. Statistical models

5.4.1. Primary analysis

Overall response rate

Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement) will be calculated [Clopper and Pearson 1934]

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

Overall response will be determined using only target, non-target, and new lesions, using the criteria specified in the protocol.

Table 5-3 Evaluation of Overall Response for Subjects

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression, death, or withdrawal of consent, whichever occurs first. Best overall response will be determined programmatically based on the investigator's assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after enrollment for a minimum of 49 days.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement, the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered NE.

Confirmation Criteria:

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.
- Confirmed best overall response will be determined programmatically based on RECIST 1.1.

5.4.2. Secondary analysis

Kaplan-Meier estimates

An estimate of the survival function in each drug combination will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment drug combination will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence

intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula.

Progression free survival will be using ONCTTE dataset and overall survival will be using ONCSURV dataset respectively.

5.5. Rule of exclusion criteria of analysis sets

Not applicable

6. Reference

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