NOVARTIS

Clinical Development

DRB436 (GSK2118436) /Dabrafenib

CDRB436B2202 (BRV116521)

An Open-label, Multicenter, Corollary Study of Pre-Operative Therapy with Dabrafenib and the Combination of Dabrafenib with Trametinib in Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain

Statistical Analysis Plan (SAP)

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Document type:	SAP Documentation
Document status:	Final 1.0
Release date:	08-Apr-2017
Number of pages:	20

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSR	Central serous retinopathy
CTCAE v4.0	v4.0 Common Terminology Criteria for Adverse Events, version 4.0
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event(s)
ULN	Upper limit of normal
US/USA	United States

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CDRB436B2202 (BRV116521), a phase IIB, open-label, multicenter, corollary study of pre-operative therapy with dabrafenib and the combination of dabrafenib with trametinib in subjects with BRAF mutation-positive metastatic melanoma to the brain. This SAP will also be used for the final analysis.

The content of this SAP is based on protocol CDRB436B2202 (BRV116521) Amendment version 03. All decisions regarding interim, primary and final analyses, as defined in the SAP document, have been made prior to database lock.

1.1 Study design

This is a global, multi-center, open-label study that will be conducted in up to 30 evaluable subjects with resectable, BRAF V600E or V600K mutation-positive metastatic melanoma to the brain. Subjects in Cohort A will receive dabrafenib orally 150 mg twice daily (BID) for 7 to 14 days prior to surgery (Cohort A); Subjects in Cohort B (the second cohort of 2 cohorts) will receive the combination of dabrafenib 150 mg BID and trametinib 2 mg once daily for 7 to 14 days prior to surgery (Cohort B).

The primary endpoints in this study are concentrations and distribution of dabrafenib, its metabolites hydroxyl-, carboxy- and desmethyl-dabrafenib and trametinib (Cohort B only) in parenchymal brain metastases, peripheral blood (plasma) and, when possible, in extracranial metastases. The secondary endpoints include concentrations of dabrafenib and its metabolites in cerebrospinal fluid (CSF) samples, changes in MAPK pathway markers and changes in the radiographic characteristics of the tumors. The efficacy endpoints are changes from baseline to pre-surgery in the sum of the longest diameters of intracranial target lesions, maximum change from baseline in the sum of longest diameters of unresected intracranial target lesions, overall extracranial response rate in unresected lesions and overall survival.

1.2 Study objectives and endpoints

Objective	Endpoint
Primary	
To determine levels and tissue distribution of dabrafenib, its metabolites and trametinib in parenchymal brain metastases peripheral blood (plasma) and, when possible, in extracranial metastases within two cohorts of subjects with BRAF V600E/K mutation-positive metastatic melanoma to the brain following pre-operative treatment.	Concentrations and tissue distribution of dabrafenib, its metabolites hydroxy-, carboxy- and desmethyl-dabrafenib and trametinib (Cohort B only) in parenchymal brain metastases, peripheral blood (plasma) and, when possible, in extracranial metastases.
Secondary	
Determine the levels of dabrafenib, its	Concentrations of dabrafenib, its metabolites

Objective	Endpoint
metabolites and trametinib in the CSF in subjects who undergo resection of BRAF V600E/K mutation-positive metastatic melanoma to the brain following pre-operative treatment	hydroxy-, carboxy- and desmethyl-dabrafenib) and trametinib (Cohort B only) in CSF samples.
Determine the activation status of the MAPK pathway following pre-operative treatment in resected brain and, when available, extracranial metastases. Activation of the MAPK kinase pathway will also be determined in samples of readily accessible extracranial metastases obtained prior to starting treatment.	Changes in MAPK pathway markers in paired extracranial biopsies taken pre-treatment, during craniotomy, and at disease progression, and changes in markers between post-operative intracranial and extracranial biopsies, when data is available.
Comparison of pharmacokinetics and pharmacodynamics to tumor response.	Changes in the radiographic characteristics of the tumors will be compared to (1) levels of dabrafenib, its metabolites and trametinib (where appropriate) in the brain metastases, plasma, and CSF, and (2) MAPK pathway activation status in tumors at the time of surgery. When available, results will also be compared to the analysis of early clinical responses in extracranial metastases, as determined by the PET-CT imaging.
To evaluate efficacy of study treatment in resected and unresected lesions.	• change from baseline to pre-surgery in the sum of the longest diameters of intracranial target lesions, • maximum change from baseline to pre-surgery in the sum of longest diameters of unresected intracranial target lesions, • overall extracranial response rate in unresected lesions, and • overall survival
To characterize the safety profile of study treatment in subjects with melanoma brain metastases.	Safety as measured by clinical assessments including vital signs and physical examinations, 12-lead electrocardiograms (ECG), echocardiogram (ECHO), chemistry and hematology laboratory values, and adverse events (AEs).
Exploratory	
To characterize the prevalence of BRAF and other mutations in melanoma brain metastases and extracranial metastases when available.	Quantitative analysis of DNA from the brain and extracranial metastases to determine the degree of concordance of BRAF mutations between the two samples. Additional mutations found in the analysis of tumor samples will be summarized.
To evaluate the baseline and changes in the expression and activation of proteins and transcriptional cell signaling networks, including the MAPK kinase pathway, in readily accessible extracranial metastases when available in patients treated with dabrafenib and dabrafenib plus trametinib and compare changes where appropriate.	The expression and activation of protein signaling pathways and transcriptional networks, including the MAPK pathway, will be evaluated when available in extracranial biopsies taken pre-treatment, at/near the time of craniotomy, and at disease progression to understand changes induced by the given treatments and their correlation with other molecular features (i.e. mutations) and treatment outcomes.
Compare the status of protein and transcriptional signaling pathways, including the the MAPK kinase	The expression and activation of protein signaling pathways and transcriptional networks, including the

Objective	Endpoint
pathway, in the brain metastases and readily accessible extracranial metastases when available.	MAPK pathway, in intracranial and, when available, extracranial biopsies collected at/near the time of craniotomy, and/or at disease progression, will be compared to identify differential molecular features and treatment effects. Results will also be compared to the analysis of early clinical responses in extracranial metastases, as determined by the PET-CT imaging, and drug levels in blood and tissue samples.

Since study is terminated with 6 enrolled patients, a short close-out CSR will be produced. The planned objectives and endpoints will not be fully analyzed.

2 Statistical methods

2.1 Data analysis general information

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

Data included in the analysis

All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'continuing at the cut-off date'. 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 cut-off date for the final analysis of study data will be established at the end of the study when all patients have been followed for survival and new anti-cancer therapy for 2 years from permanently discontinuing study treatment until death or the consent is withdrawn.

General analysis conventions

Pooling of center: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small size of centers, no center effect will be assessed.
Qualitative data (e.g. gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g. age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.1 General definitions

Investigational drug and study treatment

The investigational drug refers to dabrafenib or trametinib.

The study treatment refers to dabrafenib and combination of dabrafenib with trametinib.

Study treatment component refers to dabrafenib or trametinib.

Treatment

For presentation in the outputs, treatment refers to

Cohort A : Dabrafenib prior to surgery

Cohort B : Dabrafenib + Trametinib prior to surgery

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a nonzero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) eCRF. The date of first administration of study drug will also be referred as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as is the last date when a nonzero dose of investigational drug is administered and recorded on DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

Study day

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

The study day is defined as:

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

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

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

Time unit

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

Baseline

Baseline is defined as the most recent non-missing value prior to the first dose of study treatment.

On-treatment assessment/event and observation periods

The overall observation period will be divided into three mutually exclusive segments:

Pre-treatment period is defined as from day of patient's informed consent to the day before first administration of study treatment

On-treatment period is defined as from date of first administration of study treatment to 30 days after date of last actual administration of study treatment (including start and stop date)

Post-treatment period is defined as starting at day 30+1 after last administration of study treatment.

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

Safety summaries (tables, figures) include data from the pre-treatment period (to display the baseline status e.g. for ECG) and the on-treatment period, i.e. data from the post-treatment period with the exception of deaths should not be included unless requested from Health Authorities or external committees.

In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period, the so-called ***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 are to be flagged.

Windows for multiple assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation).

Last contact date

As a short close-out CSR will be produced, survival data will not be analyzed, this is not applicable.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive at least one dose of study treatment. The FAS will be used for summaries of baseline characteristics and all efficacy analyses unless otherwise specified.

Safety Set

The Safety Set includes all patients who received at least one dose of study treatment. All safety data will be analyzed using the Safety Set. In this study, the FAS and safety set are identical.

Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PAS) includes all patients who provide at least one evaluable PK concentration.

The PAS will be used in the analysis of PK data. Any samples missing collection date or time, or missing associated study drug dosing date or time will be excluded.

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, biomarker 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.

2.3 Patient disposition, demographics and other baseline characteristics

The 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 cohorts. Categorical data (e.g. gender, age groups >= 65, < 65, race, ethnicity, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, Body Mass Index (BMI)) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

BMI will be calculated using baseline height and baseline weight:

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

All demographic data and other baseline characteristics (alcohol history, smoking history, etc.) will be listed by patient using FAS.

Patient disposition

Subject disposition will be summarized using the FAS by cohorts.

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

A summary of study treatment status will be provided. This display will show the number and percentage of patients who discontinued study treatment or has treatment ongoing or completed the study 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.

Analysis sets

The number and percentages (based on the total number of FAS patients) of patients in each analysis set (defined in Section 2.2) will be summarized.

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

2.4.1 Study treatment / compliance

Dose administration data will be summarized by cohorts and by pre-craniotomy phase and post-craniotomy phase using the Safety Set.

In addition, a listing of exposure to dabrafenib, dabrafenib and trametinib 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 the investigational drugs:

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

The last date of exposure to study treatment is the latest of the last dates of exposure to investigational drug.

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries based on intervals and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time.

2.4.2 Prior, concomitant and post therapies

Not applicable.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

As a short close-out CSR will be produced, summary analyses will not be performed. The concentration and distribution (when applicable) of dabrafenib, dabrafenib metabolites and trametinib (Cohort B only) will be listed for each cohort by tissue type (i.e., parenchymal brain metastases, optional assessment of extracranial metastases, plasma) and by pre-craniotomy phase and post-craniotomy phase. Both absolute concentrations and ratios relative to plasma will be determined for the different sample types, if data permit.

2.5.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.5.3 Handling of missing values/discontinuations

Missing values for any PK, and tissue concentrations and distribution (when applicable) will not be imputed and will be treated as missing. Below the limit of quantitation (BLQ) values (<1 ng/mL for a 50-µL aliquot of human plasma for dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib and <5 ng/mL for a 25-µL aliquot of human plasma for carboxy-dabrafenib) will be set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. BLQ values (<5 ng/g for dabrafenib and hydroxy-dabrafenib and <30 ng/g for desmethyl-dabrafenib for a 50 µL aliquot of tissue homogenate) for tissue concentrations and distribution (when applicable) and trametinib (<5 ng/g for a 50 µL aliquot of tissue homogenate) (Cohort B only) in the measured tissues (i.e., parenchymal brain metastases, optional assessment of extracranial metastases) will be set to zero by the Bioanalyst.

Concentrations measured in CSF sample 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.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary objective(s)

As a short close-out CSR will be produced, analyses will not be performed for secondary endpoints. The concentration of dabrafenib, dabrafenib metabolites and trametinib (Cohort B only) in CSF will be listed for each cohort by pre-craniotomy phase and post-craniotomy phase. Both absolute concentrations and ratios relative to plasma will be determined for the different sample types, if data permit.

2.8 Safety analyses

All safety analyses will be based on the safety set. Summaries will be sorted and displayed by cohorts.

2.8.1 Adverse events (AEs)

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.

In AE summaries, the primary system organ class (SOC) will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

The following AE summaries will be produced: AEs by SOC, PT and maximum grade, summarized by relationship to study drug, seriousness, leading to treatment discontinuation, in addition, a summary of serious adverse events with number of occurrences will be produced.

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

Adverse events of special interest (AESIs) are defined as AEs within the following categories/groupings of PTs:

- Cutaneous squamous cell carcinoma (including keratoacanthomas)
- Treatment emergent malignancies (excluding cuSCC, basal cell carcinoma)
- Pyrexia
- Uveitis
- Renal failure/acute renal failure
- Pancreatitis

- Hypersensitivity
- Hyperglycaemia

AESIs are defined at the project level and may be updated based on emergent data to reflect new AESIs of interest at the time of analysis.

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.

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

2.8.2 Deaths

Separate summaries for on-treatment death and all deaths on-treatment and post-treatment will be produced by system organ class and preferred term. All deaths will be listed, post treatment deaths will be flagged.

Note: The death summaries cover subjects from the Safety Set.

2.8.3 Laboratory data

As a short close-out CSR will be produced, data will not be summarized and listed.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

As a short close-out CSR will be produced, data will not be summarized and listed.

2.8.4.2 Vital signs

As a short close-out CSR will be produced, data will not be summarized and listed.

2.9 Pharmacokinetic endpoints

Please refer to Section 2.5 and Section 2.7 for primary and secondary PK-related endpoints.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

As a short close-out CSR will be produced, biomarker data will not be summarized. The biomarker data will be listed, if data permit.

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

No formal interim analysis is planned for this study.

3 Sample size calculation

3.1 Primary analysis

For the objective of estimating the levels of dabrafenib its metabolites, and trametinib in brain metastases, the average level for the parent drug and each metabolite along with the range and 95% confidence interval for the brain metastases, extracranial metastases, and plasma will be reported. A sample size of 15 patients per cohort was chosen to characterize concentrations with reasonable precision (within 0.7 standard deviation) within each cohort. The correlation and corresponding 95% confidence interval between concentrations in the brain metastases and concentrations in the plasma, and in the optional extracranial metastases and CSF, for the parent drug and each metabolite will also be estimated. Additionally, the ratio between the concentrations in the brain metastases and in the extracranial metastases and the plasma concentrations within each subject for each metabolite will be estimated and summarized with 95% CI's.
Due to the difficulty in recruiting patients, this study was terminated early, 6 patients were enrolled to study at termination of study.

3.2 Power for analysis of key secondary variables

Not applicable.

4 Change to protocol specified analyses

- The primary endpoints and secondary endpoints will not be analyzed as in protocol.
- Clinical laboratory data, vital signs, 12-lead ECG, and ECHO/MUGA scan data will not be summarized and listed.

5 Appendix

This will be used later for drafting CSR Appendix 16.1.9.

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for dabrafenib:

Scenario 1: If the dose end date is completely missing and there is no EOT 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 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)

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 date imputation

The following missing dates will not be imputed

- Missing AE start dates
- AE start dates missing the year
- Partial/missing AE end dates

For other type of missing dates, rules specified in Tables 5-1 to 5-3 will be used

Table 5-1 AE/Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY

	Day	Month	Year
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 5-2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The legend to the above table is shown in Table 5-3.

Table 5-3 Imputation algorithm legends

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

Few examples are shown in Table 5-4.

Table 5-4 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
ddNOV2001	20OCT2001	After	(A)	01NOV2001

5.1.3 Concomitant medication date imputation

5.1.3.1 Prior therapies date imputation

Start date: The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that: for scenario (B) will be replaced to be start date of study drug -1.

End date:

- Imputed date = min (reference end date, DEC 31), if month and day are missing.
- Imputed date = min (reference end date, last day of the Month), if day is missing.
- Reference end date will be start date of study drug.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date. If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date

5.1.3.2 Post therapies date imputation

Start date:

- If Day is missing, then impute to the max (reference start date, first day of the month).
- Day and month are missing then impute to the max(reference start date, Jan 1)
- Reference start date will be last date of study treatment administration + 1.

End date: No imputation

5.1.3.3 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.

Missing death date

All dates must be completed with day, month and year. For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute max [(1 mmm-yyyy), min(last contact date+1 , cutoff date)].
- If both day and month are missing, then impute max [(1 Jan-yyyy, min (last contact date +1, cutoff date)].

Will the initial date of relapse, PD, or failed to respond to frontline therapy be collected on the "prior antineoplastic therapy" page?

5.2 AEs coding/grading

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

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

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

Not applicable.

5.4 Statistical models

Not applicable.

6 Reference

None.

NOVARTIS

Clinical Development

DRB436(GSK2118436)/Dabrafenib

CDRB436B2202 (BRV116521)

An Open-label, Multicenter, Corollary Study of Pre-Operative Therapy with Dabrafenib and the Combination of Dabrafenib with Trametinib in Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain

Tables, Figures and Listings (TFL) Shells- CSR deliverables

Author(s): PPD Contract Statistician; PPD Trial Statistician

Document type: RAP Document: TFL shells

Document status: Final 1.0

Release date: 17-July-2017

Number of pages: 50

Document History - Changes compared to previous version

Version	Date	Changes

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1 General guidance

1.1 Document headers

The following header will be used for all tables, listings and figures in sections 14 and 16 outlined in this document: CDRB436B2202

1.2 Presentation of table numbering and titles within this document

In practice, the numbering and title for all tables and listings in sections 14 and 16 defined in this document will be of the following formats respectively:

```
                Table XX.X-X.X
Title Title Title Title Title Title
                Population
              Listing XX.X-X.X
Title Title Title Title Title Title
                Population
```

1.3 Treatment group labels and ordering

The following treatment labels will be used for all tables, listings and figures in the order provided here:

- Treatment group label 1

```
Cohort A     Cohort B   All subjects
```

1.4 Distribution logistics

Details on in-text tables are added in section 3.1

2 Overall table of contents for statistics and programming output

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3 Shells and specification

3.1 Shells and specifications for sections 10, 11 and 12 of the CSR (Text tables and figures)

Section 10 Study Subjects

Table 10-1 Subject disposition (FAS)

Please use the same shell as Table 14.1-1.1

Source: Table 14.1-1.1

Table 10-2 Analysis set (FAS)

Please use the same shell as Table 14.1-2.1

Source: Table 14.1-2.1

Section 11 Efficacy and/or PK/PD evaluation (also Health Economics, QoL etc.)

Table 11-1 Demographic (FAS)

Please use the same shell as Table 14.1-3.1

Source: Table 14.1-3.1

Section 12 Safety evaluation

Table 12-1 Duration of exposure to study drug (Safety Set)

Please use the same shell as Table 14.3-1.1

Source: Table 14.3-1.1

Table 12-2 Overview of adverse events (Safety set)

	Cohort A N=xx		Cohort B N=xx		All subjects N=xx	
Category	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Adverse events	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Fatal SAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AEs leading to discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version <xx.x>, CTCAE version <x.xx>.

Source: Table 14.3.1-1.11

Table 12-3 Adverse events, regardless of study drug relationship by primary system organ class, maximum severity and treatment group (Safety Set)

Primary system organ class	Cohort A (N=xxx) All grades n (%)	Cohort A (N=xxx) Grade ≥3 n (%)	Cohort B (N=xxx) All grades n (%)	Cohort B (N=xxx) Grade ≥3 n (%)	All Subjects (N=xxx) All grades n (%)	All Subjects (N=xxx) Grade ≥3 n (%)
-Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac disorders	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

- Primary system organ class is sorted in descending frequency, as reported in “All Subjects” and "All grades".
- A subject with multiple occurrences of an AE is counted only once in the AE category.
- A subject with multiple adverse events is counted only once in the total row.
- MedDRA version <xx.x> has been used for the reporting.

Source: Table 14.3.1-1.1

Table 12-4 Adverse events, regardless of study drug relationship by preferred term, maximum severity and treatment group (Safety Set)

	Cohort A (N=xxx)		Cohort B (N=xxx)		All Subjects (N=xxx)	
Preferred term	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
-Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Angina pectoris	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema lower limb	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bradycardia NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema peripheral	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sinus bradycardia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Tachycardia NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Preferred term is sorted in descending frequency, as reported in "All Subjects" and "All grades".
- A subject with multiple occurrences of an AE is counted only once in the AE category.
- A subject with multiple adverse events is counted only once in the total row.
- MedDRA version <xx.x> has been used for the reporting.

Source: Table 14.3.1-1.1

Table 12-5 Adverse events, suspected to be study drug related by preferred term, maximum severity and treatment group (Safety Set)

Please use the same shell as Table 12-3

Source: Table 14.3.1-1.2

Table 12-6 On-treatment deaths by preferred term (Safety Set)

Primary reason (preferred term)	Cohort A N=xx n (%)	Cohort B N=xx n (%)	All subjects N=xx n (%)
Number of subjects who died	xx (xx.x)	xx (xx.x)	xx (xx.x)

Disease Progression	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac tamponade	xx (xx.x)	xx (xx.x)	xx (xx.x)
Breast cancer	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prostate cancer	xx (xx.x)	xx (xx.x)	xx (xx.x)

MedDRA version <xx.x>.

Source: Table 14.3.1-1.3

Table 12-7 Serious adverse events, regardless of study drug relationship by preferred term, maximum severity and treatment group (Safety Set)

	Cohort A (N=xxx)		Cohort B (N=xxx)		All Subjects (N=xxx)	
Primary system organ class	All grades n (%)	Grade 5 n (%)	All grades n (%)	Grade 5 n (%)	All grades n (%)	Grade 5 n (%)
-Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac disorders	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxxxxxxxxxxxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

- Primary system organ class is sorted in descending frequency, as reported in "All Subjects" and "All grades".
- A subject with multiple occurrences of an AE is counted only once in the AE category.
- A subject with multiple adverse events is counted only once in the total row.
- MedDRA version <xx.x> has been used for the reporting.

Source: Table 14.3.1-1.5

Table 12-8 Adverse events leading to study drug discontinuation, regardless of study drug relationship by preferred term, maximum severtity and treatment group (Safety Set)

Please use the same shell as Table 12-3

Source: Table 14.3.1-1.6

Table 12-9 Non-serious adverse events (threshold = x%) by system organ class and preferred term (Safety Set)

Please use the same shell as Table 14.3.1-1.8

Source: Table 14.3.1-1.8

Shells and specifications for Sections 14 and 16 of the CSR

Section 14 Tables, figures and graphs referred to but not included in the text

Section 14.1 Demographic data

Table 14.1-1.1 Subject disposition (FAS)

	Cohort A N=xx n (%)	Cohort B N=xx n (%)	All subjects N=xx n (%)
Subject treated	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed scheduled treatment	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment ongoing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from treatment	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for discontinuation			
Reason 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completion Status			
Completed study	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from study	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for discontinuation			
Reason 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason 4	xx (xx.x)	xx (xx.x)	xx (xx.x)

- Percentage is based on N
- Reason for end of study is from CRF end of study page

Table 14.1-2.1 Analysis set (FAS)

Analysis set	Cohort A N=xx n (%)	Cohort B N=xx n (%)	All subjects N=xx n (%)
Full analysis set (FAS)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety set	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pharmacokinetic analysis set	xx (xx.x)	xx (xx.x)	xx (xx.x)

- N is the number of subjects in FAS.
- Full analysis set includes all subjects who received at least one dose of study
- Safety set includes all subjects who received at least one dose of study medication
- The Pharmacokinetic analysis set includes all subjects who provide at least one evaluable PK concentration.

Table 14.1-3.1 Demographics (FAS)

Demographic Variable	Cohort A N=xx	Cohort B N=xx	All subjects N=xx
Age (years)			
n	xx	xx	xx
Mean (SD)	xx.x(x.xx)	xx.x(x.xx)	xx.x(x.xx)
Median	xx.x	xx.x	xx.x
Min - Max	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x
Age category (years)-n (%)			
<65	xx (xx.x)	xx (xx.x)	xx (xx.x)
>= 65	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sex-n (%)			
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race-n (%)			
African American/African Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)
American Indian or Alaskan Native	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian - Central/South Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)
East Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian - Japanese Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian - South East Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)
White - Arabic/North	xx (xx.x)	xx (xx.x)	xx (xx.x)

African Heritage			
White - White/Caucasian/European Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity-n (%)			
Hispanic/Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic/Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
ECOG Performance Status-n (%)			
0	xx (xx.x)	xx (xx.x)	xx (xx.x)
1	xx (xx.x)	xx (xx.x)	xx (xx.x)
2	xx (xx.x)	xx (xx.x)	xx (xx.x)
3	xx (xx.x)	xx (xx.x)	xx (xx.x)
4	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight (kg)			
n	xx	xx	xx
Mean (SD)	xx.x(x.xx)	xx.x(x.xx)	xx.x(x.xx)
Median	xx.x	xx.x	xx.x
Min - Max	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x
Height (cm)			
n	xx	xx	xx
Mean (SD)	xx.x(x.xx)	xx.x(x.xx)	xx.x(x.xx)
Median	xx.x	xx.x	xx.x
Min - Max	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x
Body Mass Index (BMI)(kg/m^2)#			
n	xx	xx	xx
Mean (SD)	xx.x(x.xx)	xx.x(x.xx)	xx.x(x.xx)
Median	xx.x	xx.x	xx.x
Min - Max	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x

Section 14.2 Efficacy and other non-safety data (e.g. PK, PK/PD, Health Econ., QoL)

Section 14.3 Safety data

Table 14.3-1.1 Duration of exposure to study treatment (Safety Set)

	Cohort A	Cohort B	All Subjects
Duration of exposure categories (weeks)-n (%)			
< 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 - <4	xx (xx.x)	xx (xx.x)	xx (xx.x)
4 - <8	xx (xx.x)	xx (xx.x)	xx (xx.x)
8 - <12	xx (xx.x)	xx (xx.x)	xx (xx.x)
12 - <24	xx (xx.x)	xx (xx.x)	xx (xx.x)
24 - <48	xx (xx.x)	xx (xx.x)	xx (xx.x)
48 - <60	xx (xx.x)	xx (xx.x)	xx (xx.x)
>=60	xx (xx.x)	xx (xx.x)	xx (xx.x)
Duration of exposure (months)			
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x	xx.x
Q1-Q3	xx.x-xx.x	xx.x-xx.x	xx.x-xx.x
Min - Max	xx.x-xx.x	xx.x-xx.x	xx.x-xx.x

- A subject is counted in only one duration range.

Programming Note:

1. Duration of exposure in days = Last dosing date – First dosing date + 1

Table 14.3-1.2 Summary statistics of exposure of study treatment by compound (Safety Set)

Exposure variable	Dabrafenib N=xx	Trametinib N=xx
Exposure categories (weeks) -n (%)		
< 1	xx (xx.x)	xx (xx.x)
1 - <4	xx (xx.x)	xx (xx.x)
4 - <8	xx (xx.x)	xx (xx.x)
8 - <12	xx (xx.x)	xx (xx.x)
12 - <24	xx (xx.x)	xx (xx.x)
24 - <48	xx (xx.x)	xx (xx.x)
48 - <60	xx (xx.x)	xx (xx.x)
>=60	xx (xx.x)	xx (xx.x)
Duration of exposure (months)		
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x
Q1-Q3	xx.x-xx.x	xx.x-xx.x
Min - Max	xx.x-xx.x	xx.x-xx.x
Cumulative dose (mg)		
Mean (SD)	xx.x (x.xx)	xx.x (x.xx)
Median	xx.x	xx.x
Q1-Q3	xx.x-xx.x	xx.x-xx.x
Min - Max	xx.x-xx.x	xx.x-xx.x

Section 14.3.1 Displays of adverse events

Table 14.3.1-1.1 Adverse events, regardless of study drug relationship by primary system organ class, preferred term, maximum severity and treatment group (Safety Set)

Primary system organ class Preferred term	Cohort A (N=xxx) All grades n (%)	Cohort A (N=xxx) Grade ≥3 n (%)	Cohort B (N=xxx) All grades n (%)	Cohort B (N=xxx) Grade ≥3 n (%)	All Subjects (N=xxx) All grades n (%)	All Subjects (N=xxx) Grade ≥3 n (%)
Number of subjects with at least one event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac disorders						
-Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Angina pectoris	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema lower limb	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bradycardia NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema peripheral	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sinus bradycardia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Tachycardia NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version <xx.x>, CTCAE version <x.xx>.

Programming Note:

Sort SOC by alphabetical order, PTs by descending frequency in Investigational drug column of highest relevance and subgroup (e.g. subgroup with highest N).

Table 14.3.1-1.2 Adverse events, suspected to be study drug related by primary system organ class, preferred term, maximum severity and treatment group (Safety Set)

Please use the same shell as Table 14.3.1-1.1

Table 14.3.1-1.3 On-treatment deaths, by system organ class and preferred term (Safety set)

Primary system organ class Primary reason (preferred term)	Cohort A N=xx n (%)	Cohort B N=xx n (%)	All subjects N=xx n (%)
Number of subjects who died	xx (xx.x)	xx (xx.x)	xx (xx.x)
Disease Progression	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac disorders	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac tamponade	xx (xx.x)	xx (xx.x)	xx (xx.x)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Breast cancer	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prostate cancer	xx (xx.x)	xx (xx.x)	xx (xx.x)
Respiratory, Thoracic And Mediastinal Disorders	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pneumonia	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pneumonia aspiration	xx (xx.x)	xx (xx.x)	xx (xx.x)

MedDRA version <xx.x>.

Table 14.3.1-1.4 All deaths, by system organ class and preferred term (Safety set)

Primary system organ class Primary reason (preferred term)	Cohort A N=xx n (%)	Cohort B N=xx n (%)	All subjects N=xx n (%)
Number of subjects who died	xx (xx.x)	xx (xx.x)	xx (xx.x)
Disease Progression	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac disorders	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac tamponade	xx (xx.x)	xx (xx.x)	xx (xx.x)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Breast cancer	xx (xx.x)	xx (xx.x)	xx (xx.x)
Prostate cancer	xx (xx.x)	xx (xx.x)	xx (xx.x)
Respiratory, Thoracic And Mediastinal Disorders	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pneumonia	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pneumonia aspiration	xx (xx.x)	xx (xx.x)	xx (xx.x)

Includes both on-treatment deaths, and those that occurred more than 30 days after last treatment.
MedDRA version <xx.x>.

Programming Note:

1. Deaths recorded on EOT page or within 30 days of last study treatment.

Table 14.3.1-1.5 Serious adverse events, regardless of study drug relationship by primary system organ class, preferred term, maximum severity and treatment group (Safety Set)

	Cohort A (N=xxx)		Cohort B (N=xxx)		All Subjects (N=xxx)	
Primary system organ class Preferred term	All grades n (%)	Grade 5 n (%)	All grades n (%)	Grade 5 n (%)	All grades n (%)	Grade 5 n (%)
Number of subjects with at least one event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac disorders						
-Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Angina pectoris	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema lower limb	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bradycardia NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema peripheral	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sinus bradycardia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Tachycardia NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version <xx.x>, CTCAE version <x.xx>.

Table 14.3.1-1.6 Adverse events leading to study drug discontinuation, regardless of study drug relationship by primary system organ class, preferred term, maximum severity and treatment group (Safety Set)

	Cohort A (N=xxx)		Cohort B (N=xxx)		All Subjects (N=xxx)	
Primary system organ class Preferred term	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Number of subjects with at least one event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiac disorders						
-Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Angina pectoris	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema lower limb	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bradycardia NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Oedema peripheral	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sinus bradycardia	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Tachycardia NOS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version <xx.x>, CTCAE version <x.xx>.

Table 14.3.1-1.7 On-treatment deaths and serious adverse events by system organ class and preferred term (Safety Set)

Primary system organ class Preferred term	Cohort A N=xxx n (%)	Cohort B N=xxx n (%)	All subjects N=xxx n (%)
Total number of subjects affected			
Subjects affected by serious adverse events / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Number of deaths (all causes)	xx	xx	xx
Number of deaths resulting from adverse events*	xx	xx	xx
Infections and infestations			
Pneumonia			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx	xx/xx	xx/xx
Deaths causally related to treatment/all	xx/xx	xx/xx	xx/xx
Sepsis			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx	xx/xx	xx/xx
Deaths causally related to treatment/all	xx/xx	xx/xx	xx/xx
Investigations			
Platelet count decreased			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx	xx/xx	xx/xx
Deaths causally related to treatment/all	xx/xx	xx/xx	xx/xx
Weight decreased			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences causally related to treatment/all	xx/xx	xx/xx	xx/xx
Deaths causally related to treatment/all	xx/xx	xx/xx	xx/xx
etc.			

*Number of deaths resulting from adverse events corresponds to deaths resulting from serious AE causally related to treatment.
Occurrences causally related to treatment/all: all occurrences are all SAEs occurrences regardless of causality to treatment.
Deaths causally related to treatment/all: all deaths are all SAEs with fatal outcome regardless of causality to treatment.
MedDRA version <xx.x>.

Programming Note:

Sort system organ classes alphabetically; preferred terms in descending frequency in Investigational drug column of highest relevance and subgroup (e.g. subgroup with highest N).

Include only on-treatment events (as defined in SAP).

"Occurrences causally related to treatment/all": all occurrences are all SAEs occurrences regardless of causality to treatment

"Deaths causally related to treatment/all": all deaths are all SAEs with fatal outcome regardless of causality to treatment

Only subjects having at least one serious adverse event are considered.

Table 14.3.1-1.8 Non-serious adverse events (threshold = x%) by system organ class and preferred term (Safety Set)

Primary system organ class Preferred term	Cohort A N=xxx n (%)	Cohort B N=xxx n (%)	All subjects N=xxx n (%)
Total number of subjects affected			
Subjects affected by non-serious adverse events / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Blood and lymphatic system disorders			
Anemia			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Thrombocytopenia			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Infections and infestations			
Pneumonia			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Sepsis			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Investigations			
Platelet count decreased			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
Weight decreased			
Subjects affected / exposed (%)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)	xxx/xxx (xx.xx)
Occurrences (all)	xx	xx	xx
etc.			

Total numbers of subjects affected by non-serious AEs are those subjects who had at least one preferred term that met the threshold criteria.
Preferred terms with a frequency greater than 5% in any treatment arm were printed.
MedDRA version <xx.x>.

Programming Note:

Threshold defined greater than 0 and less or equal to 5% (default EUDRACT/CT.gov: 5%)

Total number of subjects affected by non-serious AE is calculated back once the threshold is applied

Preferred terms with a frequency greater than 5% in at least one treatment arm (including the "all subjects") are printed for all treatment arms even if in some arms the threshold criteria is not met (this is different from standard AE displays).

Only subjects having at least one non-serious adverse event are considered.

Sort SOC by alphabetical order, PTs by descending frequency in Investigational drug column of highest relevance and subgroup (e.g. subgroup with highest N).

Include only on-treatment events (as defined in SAP).

Table 14.3.1-1.9 Adverse events of special interest by system organ class, preferred term and maximum grade (Safety Set)

Primary system organ class Preferred term	Cohort A (N=xxx) All grades n (%)	Cohort A (N=xxx) Grade ≥3 n (%)	Cohort B (N=xxx) All grades n (%)	Cohort B (N=xxx) Grade ≥3 n (%)
-AESI group				
-Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AESI group 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC 1				
-Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Angina pectoris	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
……	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version <xx.x>, CTCAE version <x.xx>

Programming Note:

Please repeat for AESI categories.

The AESI are:

- Cutaneous squamous cell carcinoma (including keratoacanthomas)
- Treatment emergent malignancies (excluding cuSCC, basal cell carcinoma)
- Pyrexia
- Uveitis
- Renal failure/acute renal failure
- Pancreatitis
- Hypersensitivity
- Hyperglycaemia

Table 14.3.1-1.10 Overview of AE types (Safety Set)

Overview of Adverse events	Cohort A N=xx		Cohort B N=xx		All subjects N=xx	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Adverse events	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Fatal SAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
AEs leading to discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment-related	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version <xx.x>, CTCAE version <x.xx>.

Section 14.3.2 Listings of deaths, other serious and significant adverse events

Listing 14.3.2-1.1 All deaths (Safety Set)

Treatment : xxxxx

Country/ Center/ Subject	Age/ Sex/ Race	Date of last dose	Study day of last dose	Date of death	Study day	Primary cause of Death	econdary Cause of Death
USA/PPD /PPD	20/M/Ca	PPD	76	PPD 2000	96	Heart Failure	Heart Failure

- Study day is relative to the first day of treatment(day 1).
- Subjects who died during or within 30 days after last dose of study treatment or other deaths reported in clinical database are included.

Listing 14.3.2-1.2 Serious adverse events (Safety Set)

Treatment : xxxxx

Country/ Center/ subject	Age/ Sex/ Race	Adverse event (REPORTED / Preferred / System organ class)	Start date/ Study day	End date/ Study day	Dur. (days)	Grade	Relat. to study drug	Action taken
BEL PPD	55/M/Ca	MILD DIZZINESS / Dizziness (exc vertigo) / Nervous system disorders	PPD /9	PPD /16	8	1	Not susp	None
BEL	71/F/Ca	GASTRIC DISTRESS / Abdominal pain upper / Gastrointestinal disorders	/3	/4	2	1	Susp	None
BEL	62/F/Ca	POSITION VERTIGO / Vertigo positional / Ear and labyrinth disorders	/1	Continuing		1	Not susp	None
		GASTRIC DISTRESS / Abdominal pain upper / Gastrointestinal disorders	/3	PPD 11	9	2	Susp	2

- Relationship to study drug: Not susp=Not suspected, Susp=Suspected
- Action taken: 1 = Study treatment withdrawn, 2 = Dose reduced, 3 = Dose increased, 4 = No action, 5 = Dose interrupted/delayed, X = Not applicable, subject not receiving IP when event occurred.
- Study day is relative to the first day of treatment(day 1).
- MedDRA version <xx.x>, CTCAE version <x.xx>.

Listing 14.3.2-1.3 Adverse events leading to study drug discontinuation (Safety Set)

Treatment : xxxxx

Country/ Center/ subject	Age/ Sex/ Race	SAE	Adverse event (REPORTED / Preferred / System organ class)	Start date/ Study day	End date/ Study day	Dur. (days)	Grade	Relat. to study drug	Action taken
BEL PPD	55/M/Ca		MILD DIZZINESS / Dizziness (exc vertigo) / Nervous system disorders	PPD /9	PPD /16	8	1	Not susp	2
BEL	71/F/Ca	Yes	GASTRIC DISTRESS / Abdominal pain upper / Gastrointestinal disorders	/3	/4	2	1	Susp	2
BEL	62/F/Ca		POSITION VERTIGO / Vertigo positional / Ear and labyrinth disorders	/1	Continuing		1	Not susp	2
			GASTRIC DISTRESS / Abdominal pain upper / Gastrointestinal disorders	/3	PPD 11	9	2	Susp	2

- Relationship to study drug: Not susp=Not suspected, Susp=Suspected
- Action taken: 1 = Study treatment withdrawn, 2 = Dose reduced, 3 = Dose increased, 4 = No action, 5 = Dose interrupted/delayed, X = Not applicable, subject not receiving IP when event occurred.
- Study day is relative to the first day of treatment (day 1).
- MedDRA version <xx.x>, CTCAE version <x.xx>.

Section 16 Appendices (Safety Set and Pharmacokinetic Analysis Set)

Section 16.1.7 Randomization scheme and codes (subject identification and treatment assigned)

Not applicable.

Section 16.2.1 Discontinued subjects

Listing 16.2.1-1.1 Study disposition (Full Analysis Set)

Treatment: xxxx

Country/ Center/ Subject	Age/ Sex/ Race	Last known date on study drug/ Study day	Primary reason for end of treatment	Comments for end of treatment	Primary reason for end of study discontinuation	Comments for end of study	Did subject complete study?
PPD - This section has been excluded to protect patient privacy.							

Instructions for programmers:

Repeat listing for both treatment groups

Section 16.2.2 Protocol deviations

Not listed due to short closeout CSR.

Section 16.2.3 Subjects excluded from the efficacy analysis

Not applicable.

Section 16.2.4 Demographic data

Listing 16.2.4-1.1 Baseline demographics (Full Analysis Set)

Treatment : xxxxx

Country/ Subject identifier	Age/ Sex/ Race	Ethnicity	Weight (kg)	Height (cm)
xxx/xxxxxxx	xx/xx/xx	xxxxxxxxxxxxxx	xxx.x	xxx
xxx/xxxxxxx	xx/xx/xx	xxxxxxxxxxxxxx	xxx.x	xxx
xxx/xxxxxxx	xx/xx/xx	xxxxxxxxxxxxxx	xxx.x	xxx
xxx/xxxxxxx	xx/xx/xx	xxxxxxxxxxxxxx	xxx.x	xxx
xxx/xxxxxxx	xx/xx/xx	xxxxxxxxxxxxxx	xxx.x	xxx
xxx/xxxxxxx	xx/xx/xx	xxxxxxxxxxxxxx	xxx.x	xxx

Instructions for programmers:

Repeat listing for both treatment groups

Section 16.2.5 Compliance and/or drug concentration data if available (including Bioanalytical Data Report)

Listing 16.2.5-1.1 Dose administration record by treatment <and component> (Safety Set)

Treatment : xxxxx, <Component: component 1>

Country/ Center/ Subject	Age/ Sex/race	Scheduled Dose (mg)	Actual dose (mg)	Dose change	Dose change detail	Reason	Start date and time/ study day	End date and time/ study day
xxx/xxxx/xxxxx	xx/x/xx			Yes/No	xxxx	x	ddmmmyyyy/x	ddmmmyyyy/x
				Yes/No	xxx	x	ddmmmyyyy/x	ddmmmyyyy/x
				Yes/No	xxxx	x	ddmmmyyyy/x	ddmmmyyyy/x
				Yes/No		x	ddmmmyyyy/x	ddmmmyyyy/x
				Yes/No		x	ddmmmyyyy/x	ddmmmyyyy/x
xxx/xxxx/xxxxx	xx/x/xx			Yes/No	Reduction	x	ddmmmyyyy/x	ddmmmyyyy/x

Programming Note:

1. Repeat listing for both treatment groups

Listing 16.2.5-2.1 PK concentrations for dabrafenib and dabrafenib metabolites plasma (Pharmacokinetic Analysis Set)

Treatment: xxxxx

Tissue Type: xxxxx

Phase: xxxxxx

Country/ Center/ Subject	Age/ Sex/Race	Analyte	Visit	Sample Colected Time	Assessment Date Time	Concentration (ng/mL)	BLQ Yes/No #
xxx/xxxx/xxxxx	xx/x/xx	Dabrafenib	Day 1	Before Surgery	YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	
				After Surgery	YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	
xxx/xxxx/xxxxx	xx/x/xx		Day 1	Before Surgery	YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	
				After Surgery	YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	

Below the limit of quantitation (BLQ) values (<1 ng/mL for a 50-µL aliquot of human plasma for dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib and <5 ng/mL for a 25-µL aliquot of human plasma for carboxy-dabrafenib) have been set to zero and flagged.

BLQ values (<5 ng/g for dabrafenib and hydroxy-dabrafenib and <30 ng/g for desmethyl-dabrafenib for a 50 µL aliquot of tissue homogenate) for tissue concentrations in the measured tissues (i.e., parenchymal brain metastases, optional assessment of extracranial metastases) have been set to zero and flagged.

Listing 16.2.5-2.2 PK concentrations for dabrafenib and dabrafenib metabolites in cerebrospinal fluid (Pharmacokinetic Analysis Set)

Treatment: xxxxx

Tissue Type: xxxxx

Phase: xxxxxx

Country/ Center/ Subject	Age/ Sex/Race	Analyte	Visit	Sample Colected Time	Assessment Date Time	Concentration (ng/mL)#	BLQ Yes/No
xxx/xxxx/xxxxx	xx/x/xx	Dabrafenib	Day 1	Before Surgery	YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	
				After Surgery	YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	
xxx/xxxx/xxxxx	xx/x/xx	Trametinib	Day 1	Before Surgery	YYYY-MM-DD hh:mm	xx.xx	
					YYYY-MM-DD hh:mm	xx.xx	
				After Surgery	YYYY-MM-DD hh:mm	xx.xx	
				Sample Colected Time	YYYY-MM-DD hh:mm	xx.xx	

Concentrations measured in CSF sample below the limit of quantitation (BLQ) values (<1 ng/mL for dabrafenib, hydroxy-dabrafenib and desmethyl-dabrafenib, <5 ng/mL for carboxy-dabrafenib) have been set to zero and flagged.

Listing 16.2.5-2.3 Concentration and tissue distribution of dabrafenib and dabrafenib metabolites in brain metastases (Pharmacokinetic Analysis Set)

Treatment: xxxxx

Phase: xxxxxx

Country/ Center/ Subject	Age/ Sex/Race	Analyte	Treatment description	Assessment Date Time	Concentration (ng/g)	Sample condition	Comment
xxx/xxxx/xxxxx	xx/x/xx	xxxxxx		YYYY-MM-DD hh:mm			
		xxxxxx					xxxxxx
		xxxxxx					xxxxxx
xxx/xxxx/xxxxx	xx/x/xx	xxxx					

xxxxx xxxxx
xxxxxx xxxx

Section 16.2.6 Individual efficacy response data

Not applicable.

Section 16.2.7 Adverse event listings

Listing 16.2.7-1.1 Adverse events (Safety Set)

Treatment : xxxxx

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse event (REPORTED / Preferred / System organ class)	Start date/ Study day	End date/ Study day	Dur. (days)	Grade	Relat. to study drug	Action taken
BEL/PPD	55/M/Ca		MILD DIZZINESS / Dizziness (exc vertigo) / Nervous system disorders	PPD /9	PPD /16	8	1	Not susp	None
BEL/	71/F/Ca		GASTRIC DISTRESS / Abdominal pain upper / Gastrointestinal disorders	/3	/4	2	1	Susp	None
BEL/	62/F/Ca		POSITION VERTIGO / Vertigo positional / Ear and labyrinth disorders	/1	Continuing		1	Not susp	None
			GASTRIC DISTRESS / Abdominal pain upper / Gastrointestinal disorders	/3	PPD 11	9	2	Susp	2

- Relationship to study drug: Not susp=Not suspected, Susp=Suspected
- Action taken: 1 = Study treatment withdrawn, 2 = Dose reduced, 3 = Dose increased, 4 = No action, 5 = Dose interrupted/delayed, X = Not applicable, subject not receiving IP when event occurred.
- Study day is relative to the first day of treatment(day 1).
- MedDRA version <xx.x>, CTCAE version <x.xx>.

Programming Note:

1. Repeat listing for both treatment groups

Listing 16.2.7-1.2 Adverse events of special interest (Safety Set)

Treatment : xxxxx

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse event (REPORTED / Preferred / System organ class)	Start date/ Study day	End date/ Study day	Dur. (days)	Grade	Relat. to study drug	Action taken
BEL PPD	55/M/Ca		MILD DIZZINESS / Dizziness (exc vertigo) / Nervous system disorders / XXXXXXXXXXXXX	PPD /9	PPD /16	8	1	Not susp	None
BEL	71/F/Ca		GASTRIC DISTRESS / Abdominal pain upper / Gastrointestinal disorders / XXXXXXXXXXXX	/3	/4	2	1	Susp	None

- Relationship to study drug: Not susp=Not suspected, Susp=Suspected
- Action taken: 1 = Study treatment withdrawn, 2 = Dose reduced, 3 = Dose increased, 4 = No action, 5 = Dose interrupted/delayed, X = Not applicable, subject not receiving IP when event occurred.
- Study day is relative to the first day of treatment(day 1).
- MedDRA version <xx.x>, CTCAE version <x.xx>.