NOVARTIS

Clinical Development

Ribociclib (LEE011)

CLEE011G2301 / NCT03078751

An open label, multi-center protocol for U.S. patients enrolled in a study of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, high risk early breast cancer

Statistical Analysis Plan (SAP)
Amendment 2

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Document type: SAP Documentation

Document status: Final

Release date: 24-Feb-2020

Number of pages: 26

Document History – Changes compared to previous final version of SAP

Date	Time Point	Reasons for update	Outocme for update	Section and title impacted (Current)
31-May-2017	Before DBL	First Version		
01-May-2019	Before DBL	The trial had an early enrollment closure on 12 February 2018; the protocol was amended on April 2018.	The study is now a Phase II trial. All sections related to Efficacy analysis has been removed. Efficacy data will be summarized by a listing only.	All the sections of the earlier version has been impacted
23-Feb-2020	Before DBL	1. Add one lab param for the shift table. 2. Clarify which CRS version will be used. 3. For exposure data, GnRH agonist will be combined with ET to report.	1. Blood Creatinine was added to report. 2. Added a sentence to use the most up-to-date CRS. 3. For exposure data, GnRH was combined with ET to report.	1. Section 4.3 2. section 2.7.1.1 3. section 2.4.1

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DDFS	Distant disease-free survival
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
iDFS	Invasive disease-free survival
IRT	Interactive Response Technology
LRRFS	Loco-regional recurrence-free survival
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OS	Overall Survival
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
QoL	Quality of Life
RFS	Recurrence-free survival
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analysis for the clinical study report(s) (CSR) of study CLEE011G2301, an open label, multicenter, Phase II, U.S based study to evaluate safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, high risk early breast cancer.

The content of this SAP is based on protocol CLEE011G2301 version 02. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock and unblinding of the study data.

1.1 Study design

This was a randomized, phase III, double-blind, placebo-controlled, multi-center, international study to evaluate efficacy and safety of ribociclib with ET as an adjuvant treatment in patients with HR-positive, HER2-negative, high risk early breast cancer.

Following the protocol amendment 02, this study is now an open label, multi-center phase II conducted in the U.S only. The study has been closed to enrollment. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen). Patients randomized to placebo have to complete 30-day safety follow up after the last dose of placebo.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoint

Objective	Endpoint
Primary	
To evaluate the preliminary safety and tolerability of the ribociclib + ET in patients that were randomized to ribociclib + ET prior to the early closure of enrollment.	Tolerability and Safety of the treatment regimen based on frequency and severity of AEs, laboratory and ECG abnormalities

2 Statistical methods

2.1 Data analysis general information

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

Data included in the analysis

All data collected up to the last patient last visit will be used in the analysis.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed. Protocol deviations, number of patients in analysis populations and discontinuations from study treatment will be summarized by center.
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

Investigational drug, will refer to the ribociclib/placebo only. Whereas, ***study treatment*** will refer to ribociclib + endocrine therapy (ET) and placebo + ET. In this study, ET may include tamoxifen, letrozole, anastrozole or exemestane. For premenopausal women, ET also include GnRH agonist to suppress ovarian function. ET alone after discontinuation of the ribociclib/placebo is not considered a "study treatment".

The term investigational treatment may also be referred to as ***study treatment*** which is used througouht this document.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of investigational 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 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.

Date of first administration of study treatment

The date of first administration of study treatment will be derived as the first date on/after randomization when a nonzero dose of any component of study treatment was administered as per the (e)CRF. (Example: if randomization date is 03-Jan-2015, and 1st dose of ribociclib is administered on 05-Jan-2015, and 1st dose of ET is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015).

ET prior to and on/after randomization will be entered in the Adjuvant Endocrine Therapy eCRF page. First date on/after randomization of ET will be derived based on the start and end dates in the eCRF. (Example: randomization date is 03-Jan-2015, if ET with non-zero dose has a start date of 15-Dec-2014 and an end date on/after randomization, then first date on/after randomization of ET will be 03-Jan-2015; if ET start date is 15-Dec-2014 and end date is 02-Jan-2015, then restarts non-zero dose on 04-Jan-2015, then first date on/after randomization of ET will be 04-Jan-2015; in special cases in which start date is before randomization and end date is missing, then patient is ongoing and first date on/after randomization of ET will be date of randomization)

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of study treatment was administered as per (e)CRF. For patients who take at least one dose of ribociclib/placebo, date of last administration of study treatment is the last date when a non-zero dose of ribociclib/placebo was administered. So date of last administration of study treatment is the same as date of the last administration of investigational drug for these patients. For patients who only take ET on/after randomization but no ribociclib/placebo, date of last administration of study treatment is defined as the date of first administration of study treatment.

Study day

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

The study day is defined as:

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

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (e.g., recurrence assessment,) is the date of randomization.

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

Time unit

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

Baseline

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

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as ''baseline" assessment.

For ECGs, the study requires triplicates per time point. The average of theses measurements would be calculated for baseline. In case ribociclib/placebo dosing time is recorded on the date of first dose of study treatment along with the ECG, the last available assessment before the ricobiclib/placebo start date/time will be used for baseline.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory or collected for ECGs or vital signs, then the last value should be considered as baseline. The last value refers to the one with a larger repeated sequence number recorded in the eCRF.

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

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments, based on AE start date:

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

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

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

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and strata, they have been assigned to during the randomization procedure.

Safety

The **Safety set** includes all randomized subjects who received any study treatment (i.e. at least one dose of ribociclib/placebo or ET). Subjects will be analyzed according to the study treatment actually received.

The actual treatment received corresponds to:

- the randomized treatment if patients took at least one dose of that treatment.
- the first treatment received if the randomized treatment was never received

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-2.

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

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety set	No written inform consent	No dose of study treatment

Withdrawal of Informed Consent

Any data collected in the clinical database with a date 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 patient withdraws full consent is recorded in the eCRF.

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

2.2.1 Subgroup of interest

Efficacy

Not applicable

Safety

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. Summaries will be reported by treatment arm and for all patients and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Categorical data (e.g. gender, age groups, race, ethnicity, region, ECOG Preformance 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) will be summarized by descriptive statistics (N, mean, median, standard deviation, Q1, Q3, minimum and maximum). BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by treatment arm using the FAS. The number (%) of randomized patients included in the FAS will be presented overall and by treatment group.. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

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

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on eCRF page not completed for any study treatment component, ‘DAR’ eCRF page for ribociclib/placebo, ‘Adjuvant endocrine therapy’ eCRF page for ET and ‘GnRH (Gonadotropin-Releasing Hormone) Agonist Therapies’ eCRF page for GnRH; for ET and GnRH page, only dose administered on/after randomization will be considered)
- Primary reason for not being treated (based on “End of Treatment Phase Completion” eCRF page)

- Number (%) of patients who were treated (based on eCRF pages of each study treatment component completed with non-zero dose administered)
- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Phase' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Phase' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase' page)

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by treatment group for the FAS. Major protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by treatment group. All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by treatment group.

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

2.4.1 Study treatment adherence/ compliance

Duration of exposure, will be summarized by treatment arm, for ribociclib/placebo. Exposure summaries for ET and GnRH will also be summarized by treatment arm. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval.

Subject level listings of all doses administered on treatment (for ET, also after the treatment phase) along with dose change reasons will be produced.

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

Duration of exposure to investigational drug, control drug and combination partner

The study treatment has the following components:

- Investigational drug: ribociclib/placebo
- Combination partner
    - ET: Any of letrozole, anastrozole and exemestane and GnRH agonist

The duration of exposure to ribociclib/placebo, ET will be summarized.

Duration of exposure to ribociclib/placebo and ET (tamoxifen, letrozole, anastrozole, exemestane and GnRH agonist) during the treatment phase will be calculated as:

Duration of exposure (days) during the treatment phase = (last date of exposure during the treatment phase) – (first date of exposure on/after randomization) + 1.

The last date of exposure during the treatment phase is defined as follows for ribociclib/placebo and ET:

- For ribociclib/placebo: the last date of exposure is defined as the date of last administration of ribociclib/placebo; the first date of exposure is defined as the date of first administration of ribociclib/placebo
- For ET: the last date of exposure during the treatment phase is defined as the date of last administration of any ET on/before the last date of exposure of ribociclib/placebo; the first date of exposure is defined as the date of first administration of any ET on/after randomization.
- In rare cases in which patient does not have any ribociclib/placebo but have ET on/after randomization, the last date of exposure of ET during the treatment phase is defined as the date of first exposure of ET on/after randomization

2.4.2 Primary endpoint

The primary endpoints of this study are the tolerability and safety of the treatment regimen based on frequency and severity of AEs, laboratory and ECG abnormalities. Descriptive summaries of key safety and baseline characteristics will be provided. These include summaries of treatment duration exposure, adverse events, labs, and ECG findings. The details can be found in section 2.7.

2.4.3 Handling of missing values/censoring/discontinuations

Not applicable

2.4.4 Supportive analyses

Not applicable

2.5 Analysis of the key secondary objective

Not applicable

2.6 Analysis of secondary efficacy objective(s)

Not applicable

2.7 Safety analyses

All safety analyses will be based on the safety set.

2.7.1 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. 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 in the ribociclib + ET arm.

The following adverse event summaries will be produced by treatment arm; overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE), 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, and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will also be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

2.7.1.1 Adverse events of special interest / grouping of AEs

In this section the Adverse Events of Special Interest (AESI), safety risks as defined in the Safety Profiling Plan (SPP) and Risk Management Plan (RMP) and their targeted analyses will be described. Each risk consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical or safety interest in connection with the study treatment.

All AE grouping will be stored in the Compound Case Retrieval Strategy sheet (CRS) with clear versioning and reference to the MedDRA version used.

All AESIs will exclusively be based on adverse events only. The case retrieval sheet contains all MedDRA terms which need to be considered for case retrieval (NMQs, HLGTs, PTs, etc.). Note that certain adverse events may be reported within multiple groupings.

All AESI definitions or AE grouping need to be specified in the CRS. If a CRS update is necessary, the final version needs to be available in a reasonable time ahead of the DBL. The CRS version will be included in a footnote of the AESI tables. Table 2-5 provides AESI groupings per latest CRS. The most up-to-date version of the CRS will be used at the time of the analysis.

Table 2-5 AESI groupings

AESI grouping	MedDRA category
Anemia	SMQ
Diarrhea	SMQ
Hepatobiliary toxicity	SMQ
Infections	SMQ and SOC
Leukopenia	HLT
Nausea, emesis	HLT
Neutropenia	HLT and PT
Pulmonary embolism	SMQ and HLT
QTc interval prolongation	SMQ
Renal impairment	SMQ
Reproductive toxicity	SMQ
Thrombocytopenia	SMQ

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 compound ribociclib. 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. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

2.7.2 Deaths

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

All deaths will be listed, post treatment deaths will be flagged.

Note: “Study indication” as primary reason of death should be coded using MedDRA terms based on the diagnosis CRF field at start of study. If not coded accordingly in the database, it still must be included in the summary table. Coded reasons for deaths will then be summarized by category ‘Study indication’ and ‘Other’ (as selected by the investigator).

2.7.3 Laboratory data

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

Grading of laboratory values will be assigned programmatically as per National Cancer Institute CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

For hematology: Absolute neutrophils, Absolute granulocytes, Hemoglobin, WBC, Platelet counts, PTT.

For Biochemistry: Albumin, Alkaline phosphatase, Blood Creatinine, SGPT (ALT), Amylase, SGOT (AST, Total bilirubin, Calcium (hyper & hypo), GGT, Glucose (hyper & hypo), Lipase, Magnesium (hyper & hypo), Phosphate, Potassium (hyper & hypo), Sodium (hyper & hypo).

For both groups of laboratory tests, shift tables to compare baseline to the worst postbaseline value will be produced using CTCAE grade and normal range.

A single listing for all the laboratory parameters with grades, normal ranges and lab values flagged to indicate that the values are outside the normal range will be reported.

Liver function parameters

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

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > ULN
- TBL > 2xULN
- TBL > 3xULN
- ALP > 1.5xULN
- ALP > 2xULN
- ALP > 3xULN
- ALP > 5xULN
- ALP > 8xULN

- ALP > 10xULN
- Combined categories of ALT/AST and total bilirubin: e.g., ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (biochemistry Hy's law)

2.7.4 Other safety data

2.7.4.1 ECG data

Data handling

The study requires ECG triplicates at any assessment, so the average of the ECG parameters at that assessment will be used in the analyses. For unscheduled assessments, 15-minute windows will be applied to group assessments for averaging.

Data analysis

12-lead ECGs including PR, QRS, QT, QTcF, and RR intervals will be obtained for each subject during the study. ECG data will be read and interpreted centrally.

ECG data will be summarized by presenting summary statistics of the raw data and change from baseline by treatment group and time point. The following parameters will be assessed: QTcF, QT, PR, and QRS intervals in msec, heart rate (bpm), and RR. Shift table will be presented for QTcF and QT by treatment arm.

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

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of PR> 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New value of QRS > 120 ms

A newly occurring notable ECG value is defined as an abnormal post-baseline ECG value that is not present at baseline. Baseline is defined as the average of the last ECG measurements (triplicate) taken on or before date of first dose of study treatment. In case ribociclib/placebo dosing time is recorded on the date of first dose of study treatment along with the ECG, the last available assessment before the ricobiclib/placebo start date/time will be used for baseline. The percentage of patients having notable change from baseline ECG values is based on the number of patients with both a baseline and post-baseline assessment.

A listing of all ECG assessments will be produced by treatment arm 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.

The safety set will be used for all summary tables and individual listings.

2.7.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm) (only during screening), 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 2-6 below.

Table 2-6 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 only/low only/high and low) will be presented by treatment arm. Summary statistic for change from baseline to the worst post-baseline value (in both directions, i.e. from baseline to highest post baseline and from baseline to lowest post baseline value) will be presented by treatment arm.

A listing of all vital sign assessments will be produced by treatment arm 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 Pharmacokinetic endpoints

Not applicable

2.9 PD and PK/PD analyses

Not applicable

2.10 Biomarkers

Not applicabe

2.11 Power for analysis of key secondary variables

Not applicable

3 Change to protocol specified analyses

No change from protocol specified analysis was made.

4 Appendix

4.1 Imputation rules

4.1.1 Study drug

The following rule should be used for the imputation of the dose end date for ribociclib/placebo:

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 dose end date.

Scenario 1 should not applicable for final CSR. All patients should have EOT page complete before the Database lock for Final CSR

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.

The following rules will be used for the imputation of the dose end date for ET:

If the dose end date is completely missing and there is no death date or withdrawal from consent date, the patient is considered ongoing. The cut-off date should be used as the last date of dose. If there is death date or withdrawal from consent date, then the dose end date will be the earlier of the death date and withdrawal from consent date. After imputation, compare the imputed date with start date, if the imputed date is < start date of treatment:

Use the treatment start date

4.1.2 AE, ConMeds and safety assessment partial date imputation

Table 4-1 Imputation of partial 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 4-2 Imputation of partial end dates (AE, CM)

Missing Element	Rule (*=min(last study treatment date plus 30 days, death date, cut-off date, withdrawal of consent date))
day, month, and year	• 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 *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

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

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

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications. For completely missing end date, it will not be considered as an event date for duration of AE analysis.

The above rules will be used for imputation of AE end dates if AE start date is before last dose of study treatment. In this study, SAEs suspected to be related with study treatment or ET alone after EOT will continue to be collected. The imputation of end date of SAE during the post-treatment period will be based on the same rules by replacing end date of on-treatment period in above table with last contact date.

4.1.2.1 Other imputations

Not applicable

4.2 AEs coding/grading

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

The latest available MedDRA version at the time of the analyses will be used. The MedDRA version used will be specified in the footnote of relevant tables.

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).

4.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE version 4.03, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

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

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010) **Page 1**

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9/L	< 3.0 – 2.0 x 10^9/L	< 2.0 – 1.0 x 10^9/L	< 1.0 x 10^9/L
WBC [2] (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9/L	-
Hemoglobin [2] (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M)	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB	*(16.113 x mmol/L = g/L)*		Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9/L
Neutrophils [3]↓	10^9/L	NEUT		≥2x10^9/L	< 2.0 - 1.5 x 10^9/L	< 1.5 - 1.0 x 10^9/L	< 1.0 - 0.5 x 10^9/L	< 0.5 x 10^9/L
Lymphocytes [3]↓	10^9/L	LYM		≥1.5x10^9/L	< 1.5 - 0.8 x 10^9/L	< 0.8 - 0.5 x 10^9/L	< 0.5 - 0.2 x 10^9/L	< 0.2 x 10^9/L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9/L	> 20 x 10^9/L	-
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol/L** or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

LAB - CTC grades in Novartis Oncology (26Oct15)

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010) **Page 2**

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus[2] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	≥ LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2.5 - 2.0 mg/dL < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL < 0.6 - 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L
Calcium (corrected) [2] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [2] (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) [2] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [2] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose [2] (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [2] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [2] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [2] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [2] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride [2] ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR [2]↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time[2]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen [4]↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.
(2) = **Life-threatening consequences and/or hospitalization are not considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.
(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **≥ 1.5 x 10^9/L (lymphocytes) and ≥ 2 x 10^9/L (neutrophils) are considered as LAB CTC grade 0**
(4) = For Creatinine and Fibrinogen, the **comparison with baseline is not considered** for derivation of LAB CTC grades

LAB - CTC grades in Novartis Oncology (26Oct15)

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.

Estimated glomerular filtration rate (eGFR) will be calculated using Cockcroft-Gault formula:

$$eGFR = \frac{(140 - Age) \times Mass(in\ kilograms) \times [0.85\ if\ Female]}{72 \times Serum\ Creatinine\ (in\ mg/dL)}$$

4.4 Statistical models

Not applicable

5 Reference

1. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.
2. Hudis CA, Barlow WE, Constantino JP, et al (2007). Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol 25:2127-2132.
3. Jeruss JS, Mittendorf EA, Tucker SL, et al (2008). Combined use of clinical and pathologic staging variables to define outcomes for breast cancer patients treated with neoadjuvant therapy. J Clin Oncol 2: 246-252.