NOVARTIS

Clinical Development

LEE011/ribociclib

CLEE011A2404 / NCT02941926

COMPLEEMENT-1: An open-label, multicenter, Phase IIIb study to assess the safety and efficacy of ribociclib (LEE011) in combination with letrozole for the treatment of men and pre/postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC) with no prior hormonal therapy for advanced disease

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final

Release date: 18-Dec-2019

Number of pages: 42

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10-Nov-2016	Prior to FPFV	Creation of final version	N/A - First version	NA
17-May-2017		Creation of amendment	Section 1.1: The description of the study design was updated to reflect the updates from the protocol amendment. Extension phase was added to allow patients who still derive benefit of ribociclib-based treatment however without access to ribociclib to continue to receive treatment until EOT. Updated to clarify that goserelin is added to the treatment regimen in men/premenopausal women patients. Section 1.2: Updated to add secondary objective for Extension Phase and the associated end points. Section 2.1: Updated to describe data analysis for Extension phase. Section2.2: Safety Set in Extension phase is defined for safety analysis in the Extension phase. Section 2.3: Updated to include patient disposition in Extension Phase. Section 2.4: Goserelin was added to be one the components in study treatment. Section 2.7: Proportion of patients with clinical benefit is defined and used as secondary efficacy endpoint for the Extension Phase. Section 2.8: Updated to include Safety analysis during Extension Phase. Section 2.11: Updated to reflect changes in the PRO data collection plan as per Protocol amendment.	
15-Jun-		Creation of amendment	Section 1.1: The description of the study design was	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
2018			updated to reflect the updates from the protocol amendment 2. Section 2.1.3: Leuprolide was added in definition of study treatment. Section 2.2: Definitions of analysis sets were updated to include leuprolide. Section 2.2.5: PRO analysis set was updated to clarify that the PRO analysis set only includes female patients. Section 2.3.2: Time since initial diagnosis summary was updated for clarifications. Section 2.3.5: Enrollment by country and center will be summarized for all screened patients and the FAS. Section 2.4: Duration of exposure, dose intensity, and relative dose intensity were updated to include leuprolide. Adjusted duration of exposure was updated for clarifications. Dose interruptions were updated with clarifications. Section 2.8.5.1: Summary of ECG was updated to specify change from baseline summary and time windows was specified.	
19-Nov-2019	Prior to Core Phase DBL	Creation of amendment	Section 2.1.3 For patients who transition to the Extension Phase, on-treatment period was updated and defined as from date of first administration of study treatment to the date before the first administration of study treatment in the Extension Phase. Median follow-up time is defined as (analysis cut-off date – median treatment start date +1)/30.4375. Section 2.7.3 Censoring rules for TTP were added for clarifications.	
18-Dec-2019	Prior to Core Phase	Creation of amendment	Section 2.1.3 The on-treatment period definition was updated: Core Phase: For patients who discontinue	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
	DBL		after the Core Phase 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 any study treatment (including start and stop date). For patients who transition to the Extension Phase, on-treatment period is defined as from date of first administration of study treatment to the date of last actual administration of any study treatment in the Core Phase.	

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AE	Adverse event
AESIs	Adverse events of special interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ALP	Alkaline Phosphatase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
aBC	Advanced Breast Cancer
BOR	Best Overall Response
BMI	Body Mass Index
CBR	Clinical Benefit Rate
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage Administration eCRF pages
DI	Dose Intensity
DRL	Drug Reference Listing
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
eCRF	Electronic Case Report Form
FACT-B	Functional Assessment of Cancer Therapy – Breast
FAS	Full Analysis Set
FPFV	First Patient First Visit
HER2	Human Epidermal Growth Factor Receptor s
HLGTs	High Level Group Terms
HLT	High Level Term
HR+	Hormone Receptor Positive
IA	Interim Analysis
LPFV	Last Patient First Visit
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NMQ	Novartis MedDRA queries
ORR	Overall Response Rate
OS	Overall Survival
PDI	Planned dose intensity
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-reported Outcomes
PS	Performance Status

PT	Preferred term
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SMQs	Standardized MedDRA queries
TTP	Time to Progression
WBC	White Blood Cell
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report (CSR) of study CLEE011A2404, an open-label, multi-center, Phase IIIb study of ribociclib (LEE011) in combination with letrozole for the treatment of men and pre/postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC) with no prior hormonal therapy for advanced disease.

The content of this SAP is based on protocol CLEE011A2404 v02. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is a single-arm, Phase IIIb, open-label, multi-center study to evaluate the overall safety and tolerability and clinical efficacy of ribociclib in combination with letrozole in men and postmenopausal women with HR+, HER2- aBC and no prior hormonal treatment for advanced disease. Gonadal suppression is achieved with either goserelin or leuprolide in men and premenopausal women patients.

The study will be composed of 2 phases:

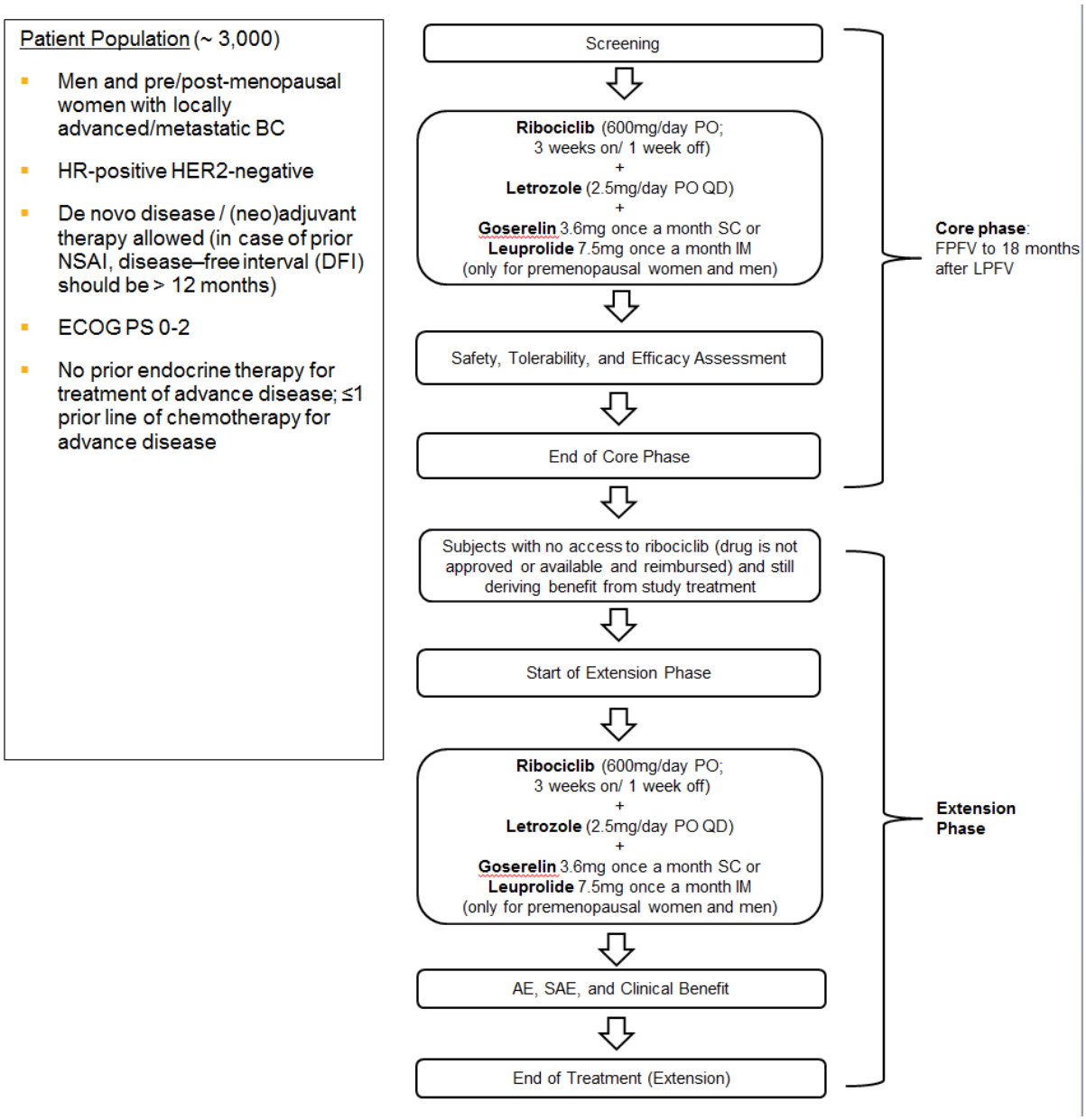
- Core Phase: from First Patient First Visit (FPFV) to 18 months after Last Patient First Visit (LPFV). During the Core Phase, safety and efficacy data (including PROs in selected subset) will be collected.
- Extension Phase: from the end of Core Phase to LPLV. In the event that study patients are still deriving benefit at the end of the Core phase and ribociclib is not approved or available and reimbursed, patients may be transitioned to this Extension phase and continue to receive the drugs until progression, intolerance, death or physician/patient decision; only safety and clinical benefit (as assessed by investigator) data will be collected.

Approximately 3,000 patients across a diverse number of sites, countries, and regions are expected to be enrolled in this trial. Study treatment will be provided until disease progression, death, unacceptable toxicities, physician's decision, patient/guardian's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical problems or until 18 months after Last Patient First Visit (LPFV), whichever event occurs first in the Core Phase and until progression, unacceptable toxicity, death, physician/patient decision, or terminated by sponsor during the Extension Phase. (See Figure 1-1)

Interim analyses (IA) may be performed periodically. The first IA is planned to be performed about 12 months after First Patient First Visit (FPFV), and periodically if needed to fulfill regulatory requests, safety updates or for publication purposes.

In this study with two phases (Core and Extension), a separate CSR is planned to be written at the end of each phase. More specifically, a CSR is planned to written at the end of the Core Phase and another CSR at the end of the Extension Phase. Only patients who are transitioned to the Extension Phase will be included in the CSR for the Extension Phase.

Figure 1-1 Study design



1.2 Study objectives and endpoints

1.2.1 Primary objective

The primary objective of this study is to further evaluate the safety and tolerability of ribociclib in combination with letrozole in men and pre/postmenopausal women with HR+, HER2- aBC who received no prior hormonal therapy for advanced disease.

To evaluate the primary objective the number (%) of patients who experienced adverse events (AEs) will be calculated for the following AE categories:

- Any AEs
- Grade 3/4 AEs
- Serious Adverse Events (SAEs)
- AEs of Special Interest (Neutropenia (including febrile neutropenia), QT prolongation, hepatobiliary AEs)
- AEs leading to discontinuation
- AEs leading to dose reduction or dose interruption
- Deaths

1.2.2 Secondary objective

The secondary objective of this study is to assess the clinical efficacy and patient-reported outcomes (PRO) of ribociclib + letrozole (+ goserelin) in Full Analysis Set.

The following efficacy endpoints as defined by RECIST1.1 will be used in the evaluation of secondary objectives:

- Time-to-Progression (TTP) based on investigators' assessment
- Overall Response Rate (ORR) for patients with measurable disease at baseline
- Clinical Benefit Rate (CBR) (including patients with complete response (CR), partial response (PR), (stable disease (SD)/Non-CR/Non-PD)>24 weeks)

In addition, PRO will be assessed using Functional Assessment of Cancer Therapy – Breast (FACT-B) instrument. (See Section 2.11)

During Extension Phase, frequency and severity of AEs & SAEs will be summarized.

The proportion of patients with clinical benefit as assessed by investigator will be reported at each scheduled visit during Extension Phase.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To evaluate the safety and tolerability of ribociclib + letrozole in men and pre/postmenopausal women with HR+, HER2- aBC who received no	• Number (%) of patients who experienced AEs, Grade 3/4 AEs & SAEs during treatment with ribociclib + letrozole

Objective	Endpoint
prior hormonal therapy for advanced disease Note: Throughout this document, perimenopausal and premenopausal status are grouped together and referred as “Premenopausal”	
Secondary	
To assess the clinical efficacy and patient reported outcomes of ribociclib + letrozole in the patient population as described above	• Time-to-Progression (TTP) (RECIST 1.1), based on investigators’ assessment • Overall response rate (ORR) as defined by RECIST 1.1 for patients with measurable disease • Clinical Benefit Rate (CBR) as defined by RECIST 1.1 (including patients with CR, PR, SD/Non-CR/Non-PD>24 weeks) • Patient Reported Outcome (PRO) using FACT-B questionnaire
To evaluate long-term safety of ribociclib + letrozole during Extension Phase	• Frequency and severity of AEs & SAEs during Extension Phase
To evaluate clinical benefit of ribociclib + letrozole as assessed by investigator during Extension Phase	• Proportion of patients with clinical benefit as assessed by investigator during Extension Phase

2 Statistical methods

2.1 Data analysis general information

Novartis and/or a designated Contract Research Organization (CRO) will perform all analyses. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

2.1.1 Data included in the analysis

The analysis cut-off date for the final analysis of the Core Phase will be established after all enrolled patients have completed at least 18 months of treatment or have discontinued study. Interim analyses (IA) are planned to be performed periodically. The first IA planned to be performed about 12 months after FPFV, and periodically if needed to fulfill regulatory requests, safety updates, or for publication purposes. 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.

Final analysis of the Extension Phase will be performed when all patients have been followed for 30 days after they have either prematurely discontinued or been discontinued from the study after completing treatment as per protocol.

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

2.1.2 General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. 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; 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).

2.1.3 General definitions

Investigational drug and study treatment

Investigational drug, will refer to the ribociclib (LEE011) only. Whereas, **study treatment** will refer to ribociclib + letrozole + goserelin/leuprolide (if applicable).

The term investigational treatment may also be referred to as **study treatment** which is used throughout in 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) Electronic Case Report Form (eCRF).

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.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the Dosage Administration eCRF. (Example: if 1st dose of ribociclib is administered on 05-Jan-2015, and 1st dose of letrozole is administered on 03-Jan-2015, then the date of first administration of study

treatment is on 03-Jan-2015). The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

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

Study day

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

The study day is defined as:

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

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

Time unit

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

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as “baseline” assessment.

In 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 multiple values are from the same laboratory (local) or collected for Electrocardiograms (ECGs) or vital signs, then the last value should be considered as baseline.

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

On-treatment assessment/event and observation periods

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

1. ***pre-treatment period***:

   Core Phase: from day of patient’s informed consent to the day before first administration of study treatment.

   Extension Phase: Not applicable.

2. ***on-treatment period***:

   Core Phase: For patients who discontinue after the Core Phase 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 any study treatment (including start and stop date). For patients who transition to the Extension Phase, on-treatment period is defined as from date of first administration of study treatment to the date of last actual administration of any study treatment in the Core Phase.

   Extension Phase: from date after the first administration of study treatment in the Extension Phase to 30 days after date of last actual administration of any study treatment

3. ***post-treatment period***:

   Core Phase: starting at day 31after last administration of study treatment for patients who discontinue after the Core Phase treatment without transitioning to the Extension Phase. Post-treatment period is not applicable for patients who transition to Extension Phase.

   Extension Phase: starting at day 31 after last administration of study treatment in the Extension Phase.

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.

Median follow-up of the study

Median study follow-up in this study will be calculated as (analysis cut-off date – median treatment start date +1)/30.4375, where 30.4375 is the average duration of a month in days. Median treatment start date is obtained by first sorting all patients in the FAS by the start date of study treatment, and then taking the date of median patient.

2.1.4 Windows for multiple assessments

In order to summarize PRO measures/performance status/vital sign/other data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

The following table provides an example how to define the time windows for Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Table 2-1 Time window for ECOG PS assessments

Assessment	Target day of assessment	Time interval
Baseline		≤ Day 1
Cycle 2 Day 1	29	Day 2 to Day 42
Cycle 3 Day 1	57	Day 43 to Day 70
Cycle 4 Day 1	85	Day 71 to Day 98
Cycle 5 Day 1	113	Day 99 to Day 126
Cycle 6 Day 1	141	Day 127 to Day 168
Cycle 8 Day 1	197	Day 169 to Day 224
Cycle 10 Day 1	253	Day 225 to Day 280
Cycle 12 Day 1	309	Day 281 to Day 350
Every 3 cycles thereafter		
Cycle k Day 1 (k = 15, 18, …, 36)	d=(k-1)*28+1	Day d-42 to Day d+41
End of Treatment		Assessment taken at the end of treatment visit

Time windows will be defined for descriptive summary of PRO data by visit and longitudinal data analysis. Data obtained at the end of treatment will be classified as other assessment in the corresponding time window. Note that only data collected under treatment (i.e. while the patient is treated) will be included in the time to definitive deterioration or longitudinal model analysis. Post-treatment data will be summarized separately. The end of treatment assessment will be included if collected within 30 days of the last dose intake. Time windows for PRO assessment (please refer to Table 2-1) is the same as the Time windows for ECOG PS assessment.

2.2 Analysis sets

2.2.1 Full Analysis Set

The Full Analysis Set (FAS) includes all patients who received at least one dose of study treatment defined as either ribociclib, or letrozole, or goserelin, or leuprolide in the Core Phase.

2.2.2 Per Protocol Set

Not applicable.

2.2.3 Safety Set in Core Phase

For this study, the definition of FAS is the same as that of Safety Set in the Core Phase.

2.2.4 Safety Set in Extension Phase

The Safety set in the Extension Phase includes all patients who received at least one dose of study medication defined as ribociclib, or letrozole, or goserelin, or leuprolide in the Extension Phase

2.2.5 Other

The patient-reported outcomes (PRO) will be collected in subgroup of patients in selected countries. The PRO Analysis Set consists of all female patients in the FAS population for whom baseline and at least one post baseline PRO measurements are available.

Patient Classification:

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

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

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent	No dose of study medication for Core Phase
Safety set in Core Phase	No written informed consent	No dose of study medication for Core Phase
PRO Analysis Set	No written informed consent	No dose of study medication or no post baseline PRO measurements for Core Phase
Safety set in Extension Phase	No written informed consent	No dose of study medication for Extension Phase

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. The date on which a patient withdraws full consent is recorded in the eCRF.

2.2.6 Subgroup of interest

The following subgroups of interest may be used at interim and/or final analysis:

- Region (Latin American, Region Europe, Asia)
- Country (countries with at least 100 patients including, but not limited to US, Canada, Italy, Spain, France, Belgium, Czech Republic)
- Prior treatments for advanced disease (no treatments vs. chemotherapy)

- Prior treatments for (neo)adjuvant (no treatments, endocrine only, chemotherapy only, both endocrine and chemotherapy)
- ECOG PS (PS 0-1 and 2)
- Liver involvement (yes vs. no)
- Lung involvement (yes vs. no)
- Lung or liver involvement (yes vs. no)
- Bone lesion only metastasis
- Other visceral/soft tissue involvement (adrenal, kidney, lymphonodes/soft tissue, etc.)
- Number of metastatic sites (0, 1, 2, ≥3)
- Age (<65, 65-<70, 70-<75, ≥75 years)
- Gender (male and female)
- Race (Asian vs. Non-Asian)
- Hormonal status at baseline (premenopausal vs. postmenopausal)

The objectives for carrying out analyses on these subgroups are to describe/characterize the treatment effect in these subgroups, to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients.

With exception of male, summary tables will only be performed if at least 100 patients are present in each subgroup.

2.3 Patient disposition, demographics and other baseline characteristics

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

2.3.1 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, race, ECOG performance status, etc.) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, body weight, etc.) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). Body Mass Index (BMI (kg/m^2) = weight (kg) / [height (m)]^2) will be calculated based on weight and height at screening.

2.3.2 Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, histological grade, stage at initial diagnosis,

stage at time of study entry, time since initial diagnosis, time from initial diagnosis to first recurrence/progression (in months), presence/absence of target and non-target lesions, HER2/Estrogen/Progesterone receptor status, number and type of metastatic sites involved.
The numbers and percentages of patients in the category defined by presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.
Time since initial diagnosis and Disease-free-interval will be summarized in months. This data will also be categorized into time intervals. Frequency counts and percentages will be presented for the number of patients in each interval.

2.3.3 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC), preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.3.4 Other

All data collected at baseline will be listed.

2.3.5 Patient disposition

Enrollment by country and center will be summarized for all screened patients and the FAS. The number (%) of treated patients included in the FAS will be presented. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

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

- Number (%) of patients who are still on-treatment (based on the ‘End of Core Treatment Phase’ page not completed);
- Number (%) of patients who discontinued the Core Treatment Phase (based on the ‘End of Core Treatment Phase’ page)
- Number (%) of patients who have entered the Extension Treatment Phase (based on the ‘End of Core Treatment Phase’ page)
- Primary reason for study treatment phase discontinuation (based on the ‘End of Core Treatment Phase’ page)

2.3.6 Patient disposition in Extension Phase

Patient disposition in the Extension Phase will be summarized using the Safety Set in Extension Phase. The following summaries will be provided:

- Number (%) of patients who are still on-treatment (based on the 'End of Extension Treatment' page)
- Number (%) of patients who discontinued the Extension Treatment Phase (based on the 'End of Extension Treatment' page)
- Primary reason for Extension Treatment Phase discontinuation (based on the 'End of Extension Treatment' page)

2.3.7 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) for the FAS. All protocol deviations will be listed.

The safety set in Extension Phase will be used for summary of listing of protocol deviations in the Extension Phase.

2.3.8 Analysis sets

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

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

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized, separately for each component of study treatment. The duration of exposure will also be presented for the study treatment and the adjusted duration of exposure will be summarized for the investigational drug and combination partner. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized.

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

The safety set in Core Phase will be used for all summaries and listings of study treatment in the Core Phase.

The safety set in Extension Phase will be used for all summaries and listings in the Extension Phase.

2.4.1.1 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 drug and the combination partner:

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

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

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries (<3, 3 to <6, 6 to <9, 9 to <12, 12 to <15, 15 to <18, ≥18 months) and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time.

2.4.1.2 Duration of exposure to investigational drug and combination partner

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

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

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

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

The last date of exposure to ribociclib is defined as the last administration of a non-zero dose of ribociclib.

The last date of exposure to letrozole is defined as the last administration of a non-zero dose of letrozole.

The last date of exposure to goserelin is defined as the last administration of a non-zero dose of goserelin + 27 days.

The last date of exposure to leuprolide is defined as the last administration of a non-zero dose of leuprolide + 27 days.

Adjusted duration of exposure (days) for ribociclib is the number of ribociclib dosing days a patient would be expected to have received per protocol, given their duration of exposure to study treatment as defined above. Since ribociclib follows a 3 weeks on , 1 week off schedule, the adjusted duration of exposure to ribociclib is the duration of exposure to study treatment minus the planned off days for ribociclib. The adjusted duration of exposure to ribociclib is therefore 21x(# completed 28 day cycles) + min(21, duration of last incompleted cycle).

For example, if the duration of exposure to ribociclib is 66 (corresponding to two cycles and 10 days), then the adjusted duration of exposure is 21*2+10=52. If the duration of exposure to ribociclib is 108 days (corresponding to three cycles and 24 days), then the adjusted duration of exposure is 21*3+21=84.

Specifically, let D1 represent the duration of exposure to study treatment as defined above. Then the adjusted duration of exposure is defined as D=21*[D1/28] + min(21, D1-28*[D1/28]) where [x] stands for the integer part of x. In this equation [D1/28] is the number of completed cycles, and D1-28*[D1/28] is the additional number of days in the last incomplete cycle (if any). For example, if D1=30 then [D1/28]=1, D1-28*[D1/28]=2, and D=23. If D1=7 then D=7; if D1=22 then D=21; if D1=28 then D=21, etc.

The adjusted duration of exposure for ribociclib will be used to calculate the dose intensity and relative dose intensity for ribociclib.

It should be noted that when calculating the adjusted duration of exposure for ribociclib, it is derived from the duration of exposure for study treatment, not from the duration of exposure for ribociclib.

Summary of duration of exposure of investigational drug will include categorical summaries based on <3, 3 to <6, 6 to <9, 9 to <12, 12 to <15, 15 to <18, ≥18 months intervals and using descriptive statistics (mean, standard deviation etc).

2.4.1.3 Cumulative dose and average daily dose

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

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

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

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

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

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

Average daily dose is defined as Cumulative dose (mg) / Number of dosing days. Drug free day(s) are not counted as dosing days.

2.4.1.4 Dose intensity and relative dose intensity

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

For ribociclib, DI is defined as

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

For letrozole, DI is defined as

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

For goserelin and leuprolide, DI is defined as

DI (mg/28 days) = Actual Cumulative dose (mg) / Duration of exposure (28 days).

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

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients as per protocol in the same dose unit and unit of time as that of the Dose Intersity. The planned dose intersity for ribociclib is 600mg/day and the planned dose intersity for letrozole is 2.5mg/day. The planned dose intensity for goserelin is 3.6 mg/28 days. The

planned dose intensity for leuprolide is 7.5 mg/28 days. Goserelin and leuprolide are admistered Day 1 of each cycle.

Relative dose intensity (RDI) is defined as follows for ribociclib and letrozole:

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

For goserelin and leuprolide, RDI is defined as

RDI = DI (mg/28days) / PDI (mg/28days).

DI and RDI will be summarized separately for each of the study treatment components, but using the duration of exposure of each of the components. In particular, while calculating DI and RDI for ribociclib, the adjusted duration of exposure for ribociclib should be used instead of the duration of exposure for ribociclib. This takes account into the 'off' days when no ribociclib is expected to be administered.

2.4.1.5 Dose reductions, interruptions or permanent discontinuations

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

'Dose changed', 'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration eCRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

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

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

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

Interruption: An interruption is defined as a 0mg dose given on one or more days during the period where a patient is not on the 'off' part of a treatment cycle, after which > 0 mg dose resumes. For patients who had dose interruption checked but never resumed non-zero dose, the dose interruption will not be counted. For example, in the sequence of 600 mg – 0 mg (dose break) – 0 mg (dose interruption) – 0 mg (dose permanently discontinuation) the 0 mg (dose interruption) will not be counted as a dose interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Due to dosing error if a patient took a dose during the dosing break with a dose that is lower than the previous dose, this will not be considered as dose reduction. For example, a patient took 600 mg from day 1-21, and on day

22-28, the patient accidently took 200 mg per day which is supposed to be a dosing break. The patient resumed 600 mg dosing on day 29. This will not be considered as dosing reduction. Only dose change is collected in the eCRF, number of reductions will be derived programmatically based on the change and the direction of the change.

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

2.4.2 Prior, concomitant and post therapies

2.4.2.1 Prior anti-cancer therapy

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

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

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

2.4.2.2 Post treatment anti-cancer therapy

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

2.4.2.3 Concomitant medications

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

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

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

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

According to Study protocol, treatment with substances which are strong inhibitors, or inducers of CYP3A4/5, or substrates of CYP3A4/5 with a narrow therapeutic window, or medications with a known risk of QT prolongation should be avoided. These substances are listed (not comprehensive and is only meant to be used as a guide) in Table 2-3.

Table 2-3 List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Avasimibe2,3, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)3, St. John's wort (hypericum perforatum)3
CYP3A4/5 substrates with NTI1	Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine
Medications with a known risk for QT prolongation4	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib, venlafaxine
Herbal preparations/ medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications

	include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the subject is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to subjects while the subject is on the study medication. If such agents are required for a subject then the subject must be discontinued study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[2] Herbal product
[3] P-gp inducer
[4] Source: www.qtdrugs.org (as of Apr 7, 2015)

However, some patients may take these substances during the treatment period and these concomitant medications will be selected via programming prior to database lock and tabulated and listed in the CSR using the appropriate analysis set (e.g. FAS). If there is an update for the list of prohibited medications (e.g. in protocol amendment), the most up-to-date list shall be used for the CSR.

Treatment with the prohibited substances mentioned above will be identified in the database as protocol deviations.

2.5 Analysis of the primary objective

The primary objective of this study is to further evaluate the safety and tolerability of ribociclib in combination with letrozole in men and postmenopausal women with HR+, HER2- aBC who received no prior hormonal therapy for advanced disease.

To evaluate the primary objective the number (%) of patients who experienced adverse events (AEs) will be calculated for the following AE categories:

- Any AEs
- Grade 3/4 AEs
- Serious Adverse Events (SAEs)
- AEs of Special Interest (Neutropenia (including febrile neutropenia), QT prolongation, hepatobiliary AEs)
- AEs leading to discontinuation
- AEs leading to dose reduction or dose interruption
- Deaths

2.5.1 Primary endpoint

The primary endpoint of this study is the number (%) of patients who experienced adverse events (AEs):

- Any AEs
- Grade 3/4 AEs
- Serious Adverse Events (SAEs)
- AEs of Special Interest (Neutropenia including febrile neutropenia, QT prolongation, hepatobiliary AEs)
- AEs leading to discontinuation
- AEs leading to dose reduction or dose interruption
- Deaths

2.5.2 Statistical hypothesis, model, and method of analysis

No statistical hypotheses will be tested in this study. The primary endpoint (number (%) of AEs, Grade 3/4 AEs and SAEs, events of special interest, AEs leading discontinuation and deaths, and AEs leading dose reduction or dose interruption) will be summarized by count and percentage in Safety Set.

2.5.3 Handling of missing values/censoring/discontinuations

All attempts will be made to ensure that the database contains full information for all safety data. No imputation will be applied for missing data except for missing dates (See Section 5.1).

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the key secondary objective

Not applicable

2.6.1 Key secondary endpoint

Not applicable.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.6.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objective of this study is to assess the clinical efficacy of ribociclib + letrozole in Full Analysis Set.

The following endpoints as defined by RECIST1.1 will be used to evaluate the secondary objectives:

- Time-to-Progression (TTP) based on investigators' assessment
- Overall response rate (ORR) for patients with measurable disease at baseline
- Clinical Benefit Rate (CBR) (including patients with CR, PR, SD/Non-CR/Non-PD > 24 weeks)

2.7.1 Secondary endpoints

Time to progression (TTP)

Time to progression is defined as time from date of start of treatment to the date of event defined as the first documented progression or death due to underlying cancer (Novartis RECIST Guideline v 3.2). Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication. When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

Overall response rate (ORR)

Overall response rate is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see Appendix 3 of the study protocol). ORR will be calculated based on the FAS in patients with measurable disease at baseline using local investigators review of tumor assessment data. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR.
Palliative radiotherapy is allowed as per protocol. If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR analyses.

Clinical benefit rate (CBR)

CBR is defined as the proportion of patients with a best overall response (BOR) of confirmed CR or PR, or SD lasting 24 weeks or longer, according to RECIST 1.1 criteria. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 23 weeks or later from enrollment, allowing for the ±1 week visit window for tumor assessments. Patients with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if they achieve a complete response or have a 'Non-CR/Non-PD'

response 23 weeks or more after enrollment. CBR will be calculated using the FAS based on the investigators' tumor assessments.

Proportion of patients with clinical benefit in the Extension Phase

Proportion of patients with clinical benefit is defined by the number of patients with clinical benefit as assessed by investigator during Extension Phase (begins after the end of the Core Phase) divided by the number of patients in the Extension Phase.

2.7.2 Statistical hypothesis, model, and method of analysis

TTP

Time to progression data will be listed and summarize. The distribution of time to progression will be estimated using the Kaplan-Meier method and the median time to progression will be presented along with 95% confidence interval (Brookmeyer and Crowley 1982) only if a sufficient number of responses are observed. The results will be plotted graphically. The 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs (Brookmeyer and Crowley 1982) at several time points (including at least 3, 6, 9, 12, 15, 18, 24 and 30 months).

ORR and CBR

ORR and CBR will be summarized using descriptive statistics (N, %) along with two-sided exact binomial 95% CIs (Clopper and Pearson 1934).

ECOG performance status

The ECOG PS scale (Table 2-4 will be used to assess physical health of patients, ranging from 0 (most active) to 5 (least active):

Table 2-4 ECOG Performance Scale

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

Frequency counts and percentages of patients in each score category will be provided by time point based on the windows defined in Section 2.1.

Proportion of patients with clinical benefit in the Extension Phase

Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits. Clinical benefit will be summarized using the Safety Set in Extension Phase.

2.7.3 Handling of missing values/censoring/discontinuations

TTP will be censored at the date of the last adequate tumor assessment if no TTP event is observed prior to the analysis cut-off date or the date when a new anti-neoplastic therapy or another investigational treatment for cancer is started, whichever occurs earlier. The censoring date will be the date of last adequate tumor assessment.

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

In particular, TTP will be censored at the last adequate tumor assessment if one of the following occurs: absence of event, the event occurred after two or more missing tumor assessments. The term “missing adequate tumor assessment” is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of “UNK”. The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event.

2.8 Safety analyses

All safety analyses for the Core Phase will be based on the safety set in Core Phase.

2.8.1 Adverse events

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

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple Common Terminology Criteria for Adverse Events (CTCAE) grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the ‘All grades’ column of the summary tables.

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

The following adverse event summaries will be produced; overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

2.8.2 Adverse events of special interest / grouping of AEs

The AEs of Special Interest (AESIs) includes: Neutropenia including febrile neutropenia, QT prolongation, and hepatobiliary AEs.

A Case Retrieval Sheet (CRS; an Excel file) with the exact composition of the adverse events groupings is to be used to map reported adverse events to the AESIs groupings (termed Specific Event Categories (SECs) in the CRS). This file may be updated (i.e. it is a living document) based on review of accumulating trial 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. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

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

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

2.8.3 Deaths

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

2.8.4 Laboratory data

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

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

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

The following listings will be produced for the laboratory data:

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

Liver function parameters

Liver function parameters of interest are total bilirubin (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 > 2xULN
    - TBL > 3xULN
    - ALT or AST > 3xULN & TBL > 2xULN
    - ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

2.8.5 Other safety data

2.8.5.1 ECG and cardiac imaging data

Data analysis

12-lead ECGs including QTcF and intervals will be obtained locally for each patient during the study. ECG data will be read and interpreted locally.

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

- 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

Summary statistics will be provided for change from baseline ECG by timepoint. Time windows for ECG assessment are the same as the time windows for ECOG PS assessment (please refer to Table 2-1). If more than one assessment is done within the same time window, the worst case will be used. A listing of all ECG assessments will be produced and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.5.2 Vital signs

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

Data handling

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

Data analysis

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

Table 2-5 Clinically notable changes in vital signs

Vital sign (unit)	**Clinically notable criteria**	
	above normal value	**below normal value**
Weight (kg)	increase >= 10% from Baseline	decrease >= 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature (°C)	>= 39.1	-

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

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

2.8.6 Safety during Extension Phase

Safety analyses for the Extension Phase will be performed on the Safety Set in Extension Phase. The assessment of safety will be based mainly on the frequency of AEs and SAEs. The following summaries will be provided:

- Adverse events (refer to Section 2.8.1)
- Adverse events of special interest (refer to Section 2.8.2)
- Deaths (refer to Section 2.8.3)

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

The PRO Analysis Set will be used for analyzing PRO data unless specified differently. The FACT-B quality of life questionnaire (see Appendix 2 of the protocol) will be used to explore patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms and treatment-related side effects in selected countries including United States, Canada, United Kingdom, France, Italy and Spain. Due to the nature of the questionnaire and validation, only females will be asked to complete this questionnaire. Scores will be added to create subscale and overall scores. A Trial Outcome Index is generated via addition of the physical well-being, functional well-being, and breast cancer subscales.

The PRO instruments are planned to be administered during screening, every cycle during the first 6 cycles, cycle 8, cycle 10, cycle 12, and every 3 cycles thereafter until the end of treatment (See Table 2.6). Collection of the FACT-B PRO have a ±3 days window unless otherwise indicated.

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

No formal statistical tests will be performed for PRO data and hence no multiplicity adjustment will be applied. Descriptive statistics will be used to summarize the subscale and overall scores at each scheduled assessment time point.

Subscale scores from the FACT-B will be displayed as mean profiles, presented over time using time windows as described in Section 2.1. Change from baseline in the subscale scores at the time of each assessment will also be summarized. Patients with an evaluable baseline

score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

Table 2-6 Patient reported outcomes collection plan

Cycle	Day	Time
Cycle 1 Day 1	1	Prior to drug dosing.
Cycles 2 to 6	Every cycle during the first 6 cycles	
Cycles 7 and subsequent	Every 2 cycles: Cycle 8,10, 12. Every 3 cycles: Cycle 15, 18, … 36)	
End of treatment	Day of the end of treatment assessment	

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

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

If more than 50% of the items are missing in a scale or subscale, the score for this scale or subscale will be considered missing for this assessment. Otherwise, the average of the non-missing items in the scale or subscale will be used to impute for the missing items when calculate the score for the scale or subscale.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

Interim analyses (IA) may be performed periodically, if needed, to fulfill regulatory requests, safety updates or for publication purposes. The IAs are planned to be performed about 12 months after FPFV, and annually thereafter for publication purposes.

Safety analyses (see Section 2.8) will be performed in IA and it will include all patients up to the data cut-off date. PRO analyses (see Section 2.11) and Efficacy analyses (see Section 2.7) will include patients who have progressed or dead, or discontinued, or who have at least 6 cycles of treatments before the cut-off date. Subgroup (see Section 2.2.5) analyses will only be performed if at least 100 patients are present in each subgroup.

3 Sample size calculation

Sample size is not based on statistical consideration. The planned sample size of approximately 3,000 patients was chosen based on the expected accrual rates and the planned duration of the trial. A large sample size could ensure the precision of the estimate of rare adverse events based on the primary objective of the trial. For example, if incidence rate of an AE is 1%, then the probability of observing at least 30 AEs out of 3,000 patients is 52.47%. For AEs with incidence rate of 2% or higher, the probability of observing at least 30 AEs out 3,000 will be greater than 99.99%.

3.1 Primary analysis

No formal analysis will be done for hypothesis testing. Safety and efficacy parameters will be summarized in appropriate population.

3.2 Power for analysis of key secondary variables

Not applicable.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study treatment

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

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the subject is considered as on-going:

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

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

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

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

Use Dec31yyyy

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

Use EOT date

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

Use last day of the Month (mm)

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

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Subjects with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

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

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

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

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

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

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

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

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

5.1.2.1 Other imputations

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

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

Incomplete assessment dates for tumor assessment

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

Applying the cut-off to tumor assessment

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

5.2 AEs coding/grading

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

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

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

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

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

Multiple lab assessments

Specific rules for defining the baseline when there are multiple lab measurements taken at the last assessment date on or before the start date of study treatment are presented below:

As a general rule the lab value among the multiple measurements with the lowest CTCAE grade will be considered as the baseline value.

Imputation Rules

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

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

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

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

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

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

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

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

5.4 Statistical models

Analysis of time to events Data

Kaplan-Meier estimates

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

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of (Brookmeyer and Crowley 1982). Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula (Collett 1994).

Analysis of Binary Data

Confidence interval for response rate

Responses will be summarized in terms of percentage rates with 100(1 − α)% confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table (Clopper and Pearson 1934).

6 Reference

1. Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time. Biometrics, 38, 29 - 41.
2. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
3. Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.