NOVARTIS

Clinical Development

LEE011/ Ribociclib

CLEE011XUS29 / NCT02732119

TRINITI-1: A Phase I/II, single arm, open-label study of Ribociclib in Combination with Everolimus + Exemestane in the Treatment of Men and Postmenopausal Women with HR+, HER2- Locally Advanced or Metastatic Breast Cancer Following Progression on a CDK 4/6 Inhibitor

Triplet with **R**ibociclib, Af**IN**Itor™ and A**I** pos**T** CDK 4/6 **I**nhibitor

Statistical Analysis Plan (SAP)

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03-Jun-20	Prior to DB lock	Team decided to remove PK parameter analysis as it will be pulished outside of CSR	Removed PK parameter details from section 3.4 and added text that PK parameter will be summarized outside of CSR	Section 3.4

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BMI	Body Mass Index
CBR	Clinical Benefit Rate
CDK	Cyclin-Dependent Kinases
Cmax	Peak blood concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose Administration Record
DCR	Disease Control Rate
DDS	DLT-determining set
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone receptor
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVR	Interactive Voice Response
IWR	Interactive Web Response
LLOQ	Lower Limit of Quantification
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCRNPD	Non-CR Non-PD
o.d.	Once Daily
ORR	Objective Response Rate
OS	Overall Survival

PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SEC	Safety Event Categories
SOC	System Organ Class
TFLs	Tables, Figures, Listings
UNK	Unknown
WHO	World Health Organization

1 Introduction

This document contains details of the statistical methods which will be used in the phase I/II clinical trial of the clinical study protocol CLEE011XUS29. This statistical analysis plan (SAP) module is prepared based on Original Protocol, CRF version 1.0. Mock tables and listing mocks are included in TFL Shell document.

Data will be analyzed by Novartis and/or designated Contract Research Organization according to the data analysis Section 10 of the study protocol which is available in Appendix 16.1.1 of the Clinical Study Report (CSR). Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 Study design

This is a multi-center, open-label, Phase I/II study consisting of two phases: Phase I and Phase II. The Phase I will be conducted in men and postmenopausal women with HR+, HER2-negative advanced breast cancer that is endocrine resistant, and a Phase II part in men and postmenopausal women with HR+, HER2 negative advanced breast cancer that is resistant to at least one endocrine therapy and who have progressed on a CDK 4/6 inhibitor.

Phase I run-in: The dose escalation part of the study is designed to estimate the MTD and/or RP2D for the combination of ribociclib when dosed continuously with everolimus and exemestane. It will consist of 3 cohorts (A and B, and C). Each cohort will enroll 3-6 evaluable patients, including at least 6 patients at the RP2D level. Between 9-24 patients are expected to be treated in the phase I part of this study. Once an optimal safety dose is determined based on tolerability, AEs, serious AE (SAEs), changes in hematology and chemistry values, vital signs, dose interruptions, reductions and dose intensity, this study will commence to a phase II design.

The study will initiate with a 2 cohort dose escalation design. Cohort A: ribociclib (250 mg daily), everolimus (2.5 mg daily) and exemestane (25 mg daily). If no DLTs are appreciated after 1 cycle, patients will then be enrolled in Cohort B: ribociclib (300 mg daily), everolimus (2.5 mg daily) and exemestane (25 mg daily). The optimal dose will then be selected and expanded in Group 1 of the Phase II part of the study.

An additional cohort, Cohort C, will be explored as a dose de-escalation cohort. A starting dose of: Ribociclib (200 mg daily), everolimus (5 mg daily) and exemestane (25 mg daily) will we explored. If DLT's are appreciated, a lower dose of: Ribociclib (200 mg daily), everolimus (2.5 mg daily) and exemestane (25 mg daily) will be explored. For further details about DLT criteria reference section 6.2.1 of the CSP.

For phase I dose cohorts are as follow:

Cohort A: Ribociclib (250 mg daily), everolimus (2.5 mg daily) and exemestane (25 mg daily).

Cohort B: Ribociclib (300 mg daily), everolimus (2.5 mg daily) and exemestane (25 mg daily).

Cohort C: Ribociclib (200 mg daily), everolimus (5 mg daily) and exemestane (25 mg daily)

Phase II: This is a multi-center open label study to evaluate the antitumor activity of the ribociclib (LEE011) +everolimus + exemestane combination in patients with advanced/metastatic HR+, HER2 negative breast cancer that have progressed on CDK4/6 inhibitor based therapy. This part of the study will be continued after the MTD/RP2D is determined in the Phase I.

A minimum of approximately 60 evaluable patients (30 per group (Group 1 and Group 2)) are required for Phase II of this study to evaluate clinical benefit rate at 24 weeks.

In each phase II group (1 and 2), if 8 or more patients show clinical benefit at 24 weeks then the null hypothesis will be rejected and the study will demonstrate significant clinical benefit.

RP2D:

Following completion of the phase I, dose escalation portion of this trial, it was determined that the RP2D to be explored in Group 1 and Group 2 of phase II are as follows:

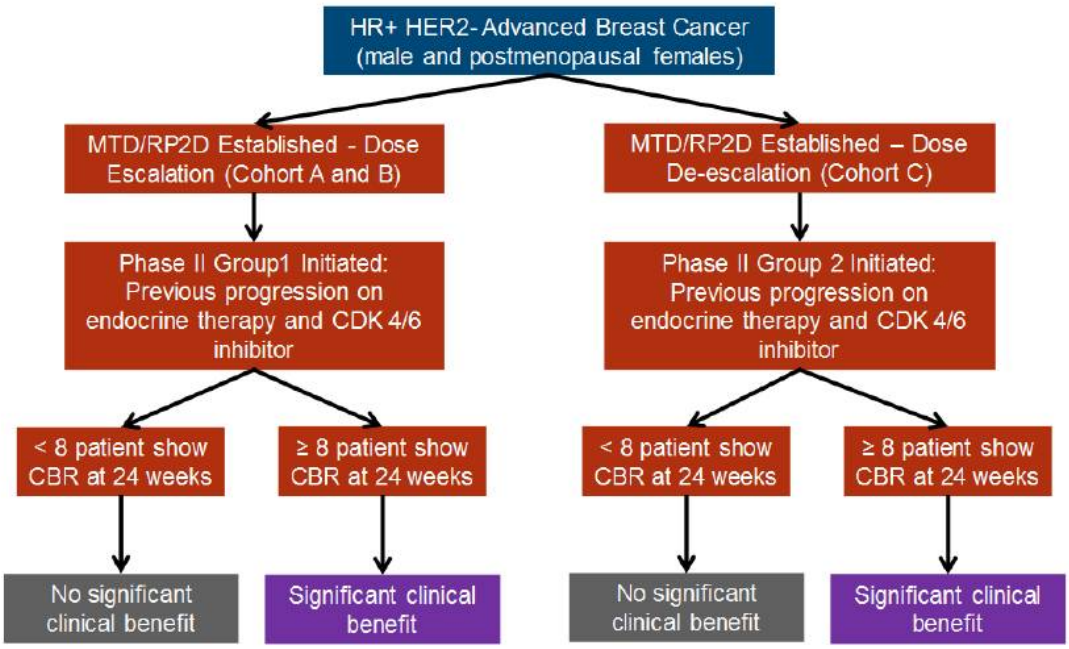
Group1: Ribociclib (300 mg daily) + everolimus (2.5 mg daily) + exemestane (25 mg daily).

Group 2:Ribociclib (200 mg daily), everolimus (5 mg daily) and exemestane (25 mg daily)

During Phase II, all patients must have progressed on any CDK 4/6 inhibitor. Prior CDK 4/6 inhibitor will be defined as disease progression while on, or within one month of discontinuing any CDK 4/6 inhibitor (i.e. palbociclib, ribociclib, or abemaciclib).

To show significant clinical benefit, currently atleast ≥ 8 patients will have to achieve CBR at 24weeks.But if number of patients enrolled in study is higher than the planned number of 33 patients (approximately 44 to 46), then the requirement for number of patients to have achieved significant clinical benefit will also increase (upto >= 10 patients).

Figure 1-1 Study Design



1.1.1 Timing of interim analyses

Not applicable.

1.1.2 Definition of end of study

The end of the study for a given patient is defined as when the patient permanently discontinues study treatment with ribociclib + everolimus + exemestane (Phase 1 and 2) and all the end of trial procedures are completed.

End of study (Last Patient Last Visit [LPLV]) will be upon completion of the follow up period for the last patient treated in the study. This will be either upon SEC of the last patient treated or after all patients have completed SEC and have been followed for at least 12 months after their first dose of study treatment, have been lost to follow-up, or withdrew consent, whichever occurs first.

Patients continuing to derive clinical benefit from study treatment, at the end of the study, in the opinion of the investigator, will be able to continue receiving ribociclib + everolimus + exemestane on a separate protocol. Ribociclib, everolimus and exemestane will be supplied by sponsor and safety will continue to be monitored.

1.1.3 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and the same assessments should be performed as described in Table 7-1 of the CSP for a discontinued or withdrawn patient. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) of the early termination of the trial.

1.2 Study objectives and end points

1.2.1 Phase I

1.2.1.1 Primary objective(s)

The primary objective of this dose escalation part of the study is to estimate the MTD(s) and/or RP2D of ribociclib in combination with everolimus and exemestane in postmenopausal women with HR+, HER2 negative advanced breast cancer.

1.2.1.1.1 End point(s) for primary objective(s)

The primary end point for the Phase I, dose escalation part of this study, is the incidence rate of Dose Limiting Toxicities (DLTs) in Cycle 1 (28 day cycle).

1.2.1.2 Secondary objective(s)

The secondary objectives for the Phase I, dose escalation part of this study, are:

- To determine the safety and tolerability based on NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 when treated with ribociclib + everolimus + exemestane continuously in subjects with HR+, HER2 negative advanced breast cancer.
- To determine the pharmacokinetic (PK) profile of everolimus and ribociclib when dosed continuously in the triplet combination.
- To assess the preliminary anti-tumor activity of the triplet combination of ribociclib + everolimus + exemestane when combination is given continuously.

1.2.1.2.1 End point(s) for secondary objective(s)

The secondary end points for the study are:

- Incidence and severity of adverse events (AE) and serious adverse events (SAE), clinical laboratory values, vital signs and electrocardiogram (ECGs), dose interruptions, reductions and dose intensity.
- PK parameters including, but not limited to, $AUC_{(0-4)}$, C_{trough}, C_{max}, accumulation ratio (Racc).
- Overall response rate (ORR), Disease Control Rate (DCR), Clinical benefit rate (CBR) based on the central assessment as per RECIST v1.1 (CBR is defined as CR, PR, SD or Non-CR-Non-PD (NCRNPD) lasting 24 weeks or longer).

Refer to Section 3.7.2.1 for definitions of ORR,DCR, and CBR. ORR, DCR, and CBR will be assessed based on the responses provided by the Investigator on centrally and locally assessed data.

1.2.2 Phase II

1.2.2.1 Primary objective(s)

The primary objective for Phase II part is to evaluate efficacy measured by Clinical benefit rate (CBR) at 24 weeks for the triple combination of ribociclib + everolimus + exemestane among patients with HR+, HER2 negative advanced breast cancer following the progression of CDK 4/6 inhibitors. CBR will be assessed based on the responses provided by the Investigator on centrally assessed data.

1.2.2.1.1 End point(s) for primary objective(s)

The primary end point of this Phase II part of this trial is CBR at week 24 (refer to Section 3.5.2.2 for definition of CBR). CBR will be assessed based on the centrally assessed tumor responses provided by the Investigator according to RECIST Version 1.1

1.2.2.2 Secondary objective(s)

The secondary objectives for the Phase II part of this trial, are:

- To determine centrally assessed Progression Free Survival (PFS)
- To determine Overall Response Rate (ORR)

- To determine Overall Survival (OS)
- To determine Duration of Overall Response (DOR)
- To evaluate time to deterioration or ECOG performance status
- To determine safety and tolerability
- To determine the PK profile of ribociclib and everolimus in the triplet combination

1.2.2.2.1 End point(s) for secondary objective(s)

The secondary end points for the Phase II part of this trial, are:

- PFS
- ORR
- OS
- DOR
- Time to definitive deterioration of ECOG performance status from baseline.
- Adverse Events (AEs), serious AE (SAEs), changes in hematology and chemistry values, vital signs, dose interruptions, reductions and dose intensity.
- PK parameters including, but not limited to, $AUC_{(0-4)}$, C_{trough}, C_{max}, accumulation ratio (R_{acc}).

Refer to Section 3.7.2.2 for definitions of ORR, OS, PFS and DOR. ORR, PFS and DOR will be assessed based on the responses provided by the Investigator on centrally and locally assessed data. Refer to Section 3.7.2.5 for definition of time to definitive deterioration.

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis and/or the designated Contract Research Organization (CRO), according to the data analysis section of the study protocol. Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation. Data from all participating centers will be combined so that an adequate number of patients are available for analysis.

All statistical analyses will be performed using SAS® Version 9.4.

The planned statistical analysis is described in Section 10 of the protocol (Appendix 16.1.1 of the CSR). Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations.

The study data will be analyzed and reported based on all patients' data up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary CSR will be reported once all patients have discontinued the study or at the end of the study, whichever occurs first.
Data will be summarized and listed by dose groups. For safety end point, all patients will be analyzed for each phase and may be pooled for analysis. The efficacy data will be analyzed for Phase I and Phase II of this study separately.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected, will not be included in any analysis, but will be reported in the CSR as separate listings.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient. Other missing data will simply be noted as missing on appropriate tables/listings.

Unless otherwise specified, all statistical tests will be performed at a two-sided significance level of 0.05 and confidence intervals will be calculated with 95% confidence.

2.1.1 General definitions

2.1.1.1 Study drug and study treatment

- For this study, the terms "investigational or study drug" refers to Ribociclib (LEE011).
- "Study treatment" refers to the triplet combination of ribociclib, everolimus and exemestane given during the course of the trial.

2.1.1.2 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a non-zero dose of study drug was administered and recorded on the Dose administration record (DAR) CRF. For the sake of simplicity, the date of first administration of study drug will also be referred as start date of study drug.

2.1.1.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on the DAR CRF.

2.1.1.4 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 and recorded on the DAR CRF. For example, if the 1st dose of study drug A is administered on 04JAN2010, and the 1st dose of its combination partner, drug B, is administered on 03JAN2010, the date of the first administration of study treatment is on 03JAN2010. For the sake of simplicity, the date of the first administration of study treatment will also be referred as the start date of study treatment.

2.1.1.5 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 and recorded on the DAR CRF. For example, if the last dose of study drug A is administered on 15APR2010, and the last dose of a combination partner, drug B is administered on 17MAY2010, the date of last administration of study treatment is then on 17MAY2010.

2.1.1.6 Study day

The study day for all assessments (both efficacy and safety) will be calculated as the difference between the date of the event (visit date, onset date of an event, assessment date, etc.) and the start date of study treatment plus one day. The first day of study treatment is therefore study day 1. The study day for all pre-treatment assessments will be calculated as the difference between the date of the event and the start of study treatment. The last day prior to study treatment intake is therefore Study Day -1.

Unless specified otherwise, the study day will be displayed in the data listings.

2.1.1.7 Baseline

Baseline (e.g. for laboratory parameters), is considered as the last available assessment or value before start of the first treatment, unless otherwise stated under the related assessment. For all relevant parameters comparisons against baseline will be presented through the report.

Baseline could be within 21 days before first treatment administration or on the same day as first treatment administration if specified pre-dose. Specific assessments may be performed more than 21 days prior to day 1 of dosing. Such cases will also be considered as baseline, if no other assessments are performed thereafter, prior to day 1 of dosing. Patients with no data

on a particular parameter before the first treatment administration have a missing baseline for this parameter.

[redacted]

For ECGs, standard triplicate 12-lead ECGs will be performed after the patient has been resting for 5-10 min prior to each time point. Triplicate ECGs should be taken approximately 2-minutes apart. The combined QTcF values from these 3 ECGs will be averaged to provide a single value for each time point.

General guidance for baseline definition:

Dependent on the variable, the baseline assessment will be done at screening (Day -21 to 1) or baseline (Cycle 1 Day 1 [C1D1]). Baseline assessments should be obtained before the first study treatment intake based on the variables. Any assessment which is obtained outside of the protocol-defined screening period will not be considered for baseline unless otherwise specified.

2.1.1.8 On-treatment assessment/event

Safety summaries and selected summaries of deaths will summarize only on-treatment assessments/events. On-treatment assessment/event is defined as any assessment/event obtained in the time interval:

Date of first administration of study treatment through the date of last administration of study treatment + 30 days, i.e. including the lower and upper limits.

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF.

If the last date of study treatment is missing, on-treatment assessments/events include any assessment/event recorded in the database and which occur after the start date of study treatment.

Data listings will include all assessments/events, flagging those which are not on-treatment assessments/events.

2.1.1.9 Last contact date

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

- All assessment dates (e.g. vital signs assessment, performance status). Note, only a true on study assessment date or patient contact date will be used. If there is a visit date without evidence of any actual assessment performed that date will not be used. No dates post cut-off will be used.
- Medication dates including study medications, concomitant medications, and anti-neoplastic therapies administered after study treatment discontinuation (with non-missing medication/procedure term).
- Adverse event dates (with non-missing verbatim AE term present).

- Last known date patient alive collected on the 'Survival information' eCRF.
- Date of discontinuation from end of treatment page and 'End of post-treatment follow-up' eCRF.

The last contact date is defined as the latest complete date from the above list or the cut-off date whichever comes first. The cut-off date will not be used for last contact date, unless an actual assessment or patient contact was performed.

Important note: imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date, except for the following: partial date's imputation is allowed to be used for event (death) and for censoring date only if coming from Survival Information page.

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

2.2 Analysis sets

2.2.1 Full analysis set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of the assigned combination of study drugs (ribociclib + everolimus + exemestane) i.e. a patient should have taken atleast one dose of each of the components from the study treatment.

2.2.2 Safety set

The Safety Set includes all patients who received at least one dose of any of the components from the investigational treatment, and have at least one valid post-baseline safety assessment.

The statement that a patient had no AEs (on the AE eCRF) constitutes a safety assessment.

2.2.3 DLT-determining analysis set

The DLT-determining set (DDS) includes all patients from the safety set in the dose escalation part who either completed a minimum exposure requirement and have sufficient safety evaluations in the first cycle or discontinued prematurely due to a dose limiting toxicity (DLT).

A patient is considered to have met the minimum exposure requirement if having received at least 75% of the planned combination doses (i.e. 21 out of 28 planned daily doses) for all compounds administered together (same day): ribociclib, everolimus and exemestane. The length of a cycle is 28 days.

Patients who do not experience a DLT during the first cycle will be considered to have sufficient safety evaluations if they have been observed for ≥28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Note: This analysis set will only use to display dose limiting toxicities for phase I.

2.2.4 Pharmacokinetic analysis set

The PK analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable PK data. The PAS will be used for summaries of PK data (tables and figures) as well as for listings of derived parameters.

2.2.5 Per-protocol set

A subset of Full Analysis Set (FAS) excluding major protocol violations.

Supportive analyses of the primary endpoint (i.e., CBR) may be performed using Per- protocol set (PPS).

[redacted]

2.2.7 Subgroup of interest

Not Applicable.

2.3 Concomitant medications with specific impact on the analysis

2.3.1 Inducers, inhibitors and substrates of CYP3A

According to the 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 in the Table 2-1. A corresponding list for programming purposes will be saved in a separate document.

However, some patients may take these substances during the treatment period so these concomitant medications will be selected via programming and tabulated and listed in the Clinical Study Report. 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 Clinical Study Report.

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

Table 2-1 List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, VIEKIRA PAK2, voriconazole
Strong CYP3A4/5 inducers	Avasimibe[2,3], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]
CYP3A4/5 substrates with NTI[1]	Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lomitapide, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, cocaine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacine, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), oxaliplatin, papayerine HCl, pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib
Herbal preparations/medications	Herbal preparations/medications known as strong inducers or inhibitors of CYP3A4/5 or those with a known risk of QT prolongation 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 patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient 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 August 23, 2017)
As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at qtdrugs.org.

3 General Strategies for Data Presentation

All categorical data will be summarized by frequencies and percentages. Wherever categorical data is missing, a 'Missing' row will be included at the bottom with frequencies and percentages presented for it.

Continuous data will be summarized with either standard descriptive statistics (i.e. the number of non-missing data points, arithmetic mean, 25th and 75th percentiles, standard deviation, minimum, median and maximum), or will be grouped into categorical data and summarized as categorical data.

All collected data will be listed.

3.1 Patient disposition, demographics and other baseline characteristics

3.1.1 Patient disposition

3.1.1.1 End of treatment phase disposition

The number of patients who are enrolled and treated as well as those who discontinued the study (along with their reasons for premature discontinuation) or are still ongoing in the study at the time of the analysis will be summarized for FAS by dose cohorts of Phase I and by groups of Phase II.

A listing of study completion by dose cohorts of phase I and groups of phase II will be produced using the FAS. Patients are considered to be ongoing if they have not discontinued due to any reason.

The possible reasons for discontinuation of study treatment are as follows:

- Adverse events
- Lost to follow up
- Physician decision
- Pregnancy

- Protocol Deviation
- Technical problems
- Subject/Guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

A listing for data on final status of the patient in the study will be provided. A data listing of screened patients who did not take study drug will be also provided with reasons for screening failure.

3.1.2 Demographic and baseline characteristics variables

Demographic and baseline characteristics data will be summarized using the FAS. All demographic and background data will also be listed.

The following variables will be summarized by dose cohorts of Phase I and by groups of Phase II:

- Age [years]
- Age categories
  - ≤40
  - >40 - ≤60
  - >60 - ≤75
  - >75
  - missing
- Sex
  - Male
  - Female
  - missing
- Race
  - Asian
  - Black
  - White/Caucasian
  - Native American
  - Pacific Islander
  - Unknown
  - Other
  - missing
- Ethnicity
  - Hispanic/latino
  - East Asian
  - Chinese
  - Japanese
  - Korean
  - Other East Asian

  - South East Asian
  - Thai
  - Malay
  - Vietnamese
  - Cambodian
  - Laotian
  - Indonesian
  - Filipino
  - Other South East Asian
  - South Asian
  - Indian
  - Pakistani
  - Other South Asian
  - West Asian
  - Turkish
  - Arabian
  - Persian
  - Lebanese
  - Other West Asian
  - Russian
  - Mixed Ethnicity
  - Not Reported
  - Unknown
  - Other
  - Missing
- Child bearing status for female patients
  - Able to bear children
  - Premenarche
  - Post menopausal
  - Sterile-of child bearing age
- ECOG PS
  - 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
  - Missing
- Body weight [kg]
- Body weight categories
  - <55

  - 55-75
  - ≥75
- Body height [cm]
- Body Mass Index (BMI) [kg/m^2]
- BMI categories
  - <30
  - ≥30

All categorical data will be summarized by frequencies and percentages. Continuous data will be summarized with standard descriptive statistics.

3.1.3 Medical history

Medical history and current medical conditions will be summarized using FAS, by dose cohorts of Phase I and by group of Phase II and will also be listed. Separate summaries will be presented for current and past medical conditions; these summaries will be presented by primary system organ class and preferred term. Medical history/current medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

3.1.4 Diagnosis and extent of cancer

For the patients in FAS, the summary statistics will be provided for the following variables for diagnosis and extent of cancer: Diagnosis of disease

- Histological grades
- Staging system used
- Stage at initial diagnosis
- Stage at study entry
- Histological grade
- Predominant histology/cytology
- Number and type of metastatic sites involved.
- Time since initial diagnosis

Time since initial diagnosis will be summarized in months. A month is defined as 365.25/12=30.4375 days. This data will also be categorized into time intervals. Frequency counts and percentages will be presented for the number of patients in each interval. The summary will be by dose cohorts of Phase I and by group of Phase II.

3.1.5 Other baseline characteristics

ER, PgR and HER2, Rb status, prior line of endocrine therapy and chemotherapy prior CDK4/6 inhibitor and duration of CDK4/6 inhibitor will also be summarized and listed using FAS, by dose cohorts of Phase I and by group of Phase II.

3.1.6 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to (within 30 days prior to first dose) and after the start of the study drug treatment will be listed by patient and summarized by ATC (Anatomical Therapeutic Chemical Classification System) term. All prior and

concomitant medication/significant non-drug therapies entered into the database will be coded using the World Health Organization (WHO) Drug Reference List dictionary, which is supplied by Novartis and used by CRO at the time of coding.

These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

The number and percentage of patients taking such treatments will be summarized for patients in the Safety Set, by dose cohorts of Phase I and by group of Phase II.

3.1.7 Prior antineoplastic therapy

Prior anti-neoplastic therapy will be listed in three separate listings: (i) medications, (ii) radiotherapy, and (iii) surgery. This summary will be provided for FAS patients by dose cohorts of Phase I and by group for Phase II.

The summary of prior anti-neoplastic medication will include the total number of regimens used at last therapy, setting of last medication, and also the time from last medication to progression, the best response at last therapy .Best Response is defined as the best recorded patient response during all previous treatment regimens, up to and including the last recorded.

The last medication is defined taking into account the end date.

All prior antineoplastic medications will also be tabulated by ATC code, preferred term by dose cohorts of Phase I and by group for Phase II.

The summary of prior anti-neoplastic radiotherapy will include a summary of radiotherapy locations, including all locations recorded for each patients. Setting, method and prior radiotherapy of bone marrow (Y/N) at last radiotherapy will also be summarized.

The summary of prior anti-neoplastic surgeries will include the time between the last surgery to start of treatment, procedure applied in last surgery and residual disease at last surgery.

A summary of post discontinuation antineoplastic medications, surgeries and radiotherapies will also be provided with recorded details.

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

3.2.1 Study treatment exposure

The following algorithm will be used to calculate the duration of study treatment exposure (in cycles and in days) for patients who takes at least 1 dose of the study treatment:

- Duration of exposure (days) to investigational drug = date of last administration of the study drug – date of first administration of the study drug + 1.

- Duration of exposure (days) to study treatment = (latest of last dates of exposure to study treatment (ribociclib, everolimus and exemestane)) – (date of first administration of study treatment (ribociclib, everolimus and exemestane)) + 1.

For patients who did not take any drug, the duration of drug exposure is by definition equal to zero.

- Cumulative Dose: Cumulative dose is defined as the total dose given to a patient during the study treatment. For patients who did not take any drug the actual cumulative dose is by definition equal to zero.
- Average Daily Dose: It is defined cumulative dose divided by the number of days the patients took the drug (excludes the no-dose period)
- Dose Intensity (DI): DI is defined as the ratio of cumulative dose and the number of days the patient should have taken the drug (includes the no-dose period).
- Planned dose intensity (PDI): PDI is defined as the ratio of total planned dose and the number of days the patient should have taken the drug [(planned dose * (last dose date – first dose date+1)].
- Relative Dose Intensity (RDI): RDI is defined as the ratio of dose intensity (DI) and planned dose intensity (PDI) based on planned dose and planned duration, expressed as percentage.

Cumulative Dose, average daily dose, DI, PDI and RDI will be calculated separately for each of the component of study treatment.

Additionally, prior duration of CDK4/6 against the duration of CDK4/6 during the study will be summarized by 25^{th} ,50^{th} (median) and 75^{th} Percentiles of duration.

3.2.2 Study treatment

The actual dose and duration (days) of ribociclib, everolimus and exemestane will be summarized by means of descriptive statistics. The summary data will be presented by dose cohorts of Phase I and by group of Phase II. The total daily doses of ribociclib, everolimus and exemestane for each patient will be summarized using descriptive statistics (e.g. mean, median, maximum and minimum doses). The exposure data for all the patients will be provided based on the Safety Set.

3.2.3 Dose change or interruptions

The number of patients who have dose change or interruptions and the reasons for such change /interruptions will be summarized by study treatment component using Safety Set. This summary will be provided by dose cohorts of Phase I and by group of Phase II.

If a patient moves from a protocol-studied dose down to a lower-than-protocol-studied dose or to the dose level being studied under the protocol but on a less frequent regimen, such changes will then be counted as reductions.

3.2.4 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations for all patients in FAS. These will be identified prior to database lock and will be listed and summarized by dose cohorts of Phase I and by group for Phase II.

Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions for all patients in FAS.

3.3 Efficacy Evaluations

3.3.1 Disease assessment

Disease assessment will be carried out in patients by radiological assessments (e.g. CT /MRI/bone scan).

All the components of the disease assessment will be listed. These components will be further assessed based on the responses provided by the Investigator on centrally and locally assessed data. The response assessment by Investigator should be based on all available data as per RECIST V1.1 guidelines.

Patients should have at least one documented measurable lesion (per RECIST v1.1) or in the absence of measurable disease, have at least one lytic or mixed (blastic/lytic) bone lesion at study entry.

Table 3-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to <10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm^2.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See CSP Section 14.2.6.

Table 3-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (<10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1]. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Table 3-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in CSP Section 14.2.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen. Further details can be found in Protocol Appendix 2.

3.3.1.1 Measurable disease

Measurable disease will be defined as the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. For more details on nodal and non-nodal lesion, refer protocol Section 14.2.4.

3.3.1.2 Responder

A patient will be called a responder if at any post baseline visit, patient is assessed to have response (PR and higher) and if the response is confirmed atleast 4 weeks apart.

3.3.1.3 Non Responder

A patient will be called a non-responder if at any baseline visit, patient is assessed to have no response (unconfirmed response of CR/PR or response of SD, PD). A patient who discontinues for any reason before the data cut-off date of the CSR without a confirmed assessment of response will be considered a non-responder. Patients with unknown or missing response, or who are treated in the study but provide no information on response at the end of treatment will also be treated as non-responders.

The non-responders will be included in the denominator while calculating percentages.

3.3.1.4 Adequate tumor response assessment

An adequate tumor response assessment is considered as disease assessment that is indicating any disease status apart from "unknown" or "not done".

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

The tumor assessment will be time slotted using the time windows displayed in Table 3-4:

Table 3-4 Time windows for tumor assessment

Time window	Planned Visit Timing	Time Window Definition
Week 8	57 (week 8)	(1,86] days ; (1, 12] weeks
Week 16	113 (week 16)	(86, 142] days ; (12, 20] weeks
Week 24	169 (week 24)	(142, 198] days; (20, 28] weeks
Week 32	225 (week 32)	(198, 282] days; (28, 36] weeks

Week 40	280 (week 40)	(282, 352] days; (36, 44] weeks
Week 48	337 (week 48)	(282, 380] days; (44, 52] weeks
Until week 48 (12 months)	X (week Y)	(X-27, X+29] days; (Y-4, Y+4] weeks
Week 60	421 (week 60)	(380, 464] days; (54, 66] weeks
Week 72	505 (week 72)	(464, 548] days; (66, 78] weeks
Week k (beyond 12 months)	X (week Y)	(X-43, X+41] days; (Y-6, Y+6] weeks

3.3.1.5 Confirmation of response

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

3.3.1.6 Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. BOR will be assessed based on the responses provided by the Investigator on centrally and locally assessed data.

The best overall response will usually be determined from response assessments undertaken while on treatment. Any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required
- SD = at least one SD assessment (or better) >6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤12 weeks after randomization/start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks).

3.4 PK evaluations

The LLOQ for ribociclib (and LEQ803) in plasma is approximately 1.00 ng/mL. The LLOQ for everolimus in whole blood is approximately 0.3 ng/mL. The LLOQ for exemestane in plasma is approximately 0.0200 ng/mL. All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings.

Only PK concentration data will be summarized for CSR. The PK parameters will be summarized outside of CSR.

3.5 Analysis of the primary objective

The primary objectives of the trial are as follows:

- **Phase I**

The primary objective of this dose escalation part of the study is to estimate the MTD(s) and/or RP2D of ribociclib in combination with everolimus and exemestane in postmenopausal women with HR+, HER2 negative advanced breast cancer.

- **Phase II**

The primary objective is to evaluate efficacy measured by Clinical benefit rate (CBR) at 24 weeks for the triple combination of ribociclib + everolimus + exemestane among patients with HR+, HER2 negative advanced breast cancer following the progression of CDK 4/6 inhibitors. CBR will be assessed based on the responses provided by the Investigator on centrally and locally assessed data.

3.5.1 Primary end point

3.5.1.1 Phase I

The primary end point for the Phase I, dose escalation part of this study, is the incidence rate of Dose Limiting Toxicities (DLTs) in Cycle 1 (28 day cycle).

3.5.1.2 Phase II

The primary end point of this Phase II part of this trial, is CBR at week 24.

3.5.2 Statistical hypothesis, model, and method of analysis

3.5.2.1 Phase I

MTD definition: The MTD is defined as the highest combination drug dosage not causing medically unacceptable, DLT in more than 33% of the treated patients in the first cycle of treatment. AEs and laboratory abnormalities considered to be DLTs are defined in Protocol Table 6-3. Only one RP2D will be tested in the Phase II.

In the dose escalation a total of 6 patients will be treated at dose-level 1 (cohort A). Patients must complete a minimum of one cycle of treatment with the minimum safety evaluation and

drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions.

- If ≤33% of patients experience a DLT in cohort A (dose level 1), the dose will be escalated to the next level cohort B (dose level +1) where 3 patients will be enrolled.
- If ≤33% patients experience DLTs in cohort B, additional 3 patients will be treated at the same dose level.
- If ≤33% patients experience a DLT in both cohorts, then the optimal treatment dose based on tolerability and safety profile will move into Phase II.
- If >33% patients experience DLTs in both cohorts, the dose will be de-escalated to the next level down.

Dose escalation and R2PD decisions will be made jointly by Steering Committee members and Novartis study personnel.

Listing and summary tables of DLT starting during the first 28 days of treatment by primary system organ class, preferred term, by dose cohort and overall for Phase I will be presented based on DLT-determining set (DDS).

3.5.2.2 Phase II

- Clinical Benefit Rate (CBR):

Clinical Benefit Rate (CBR) is defined as the proportion of patients with a complete response (CR), partial response (PR), stable disease (SD) or Non-CR Non-PD (NCRNPD) at 24 weeks as per RECIST V1.1. Thus, any instance of CR, PR, SD or NCRNPD in the first 24 weeks of the treatment, without having an instance of progressive disease (PD) will be accounted for, while calculating CBR. The instances of unconfirmed CR and/or PR will also be accounted for, while calculating CBR.

Demonstration of significant Clinical Benefit Rate (CBR) will be based on this study with at least an 80% power to test the null hypothesis that the clinical benefit rate in 24 weeks is at least 10% or less with an alternative hypothesis that this rate is above 10%.

All the other patients will be counted as not having clinical benefit.

The study is designed to test the following statistical hypothesis:

H_0 : CBR ≤ 10% vs. H_1 : CBR > 10%

The null hypothesis will be rejected and successful clinical benefit will be demonstrated if the lower limit of the 95% confidence interval is greater than at least 0.10. Thus, if 8 or more patients show clinical benefit at 24 weeks then the null hypothesis will be rejected and significant clinical benefit will be demonstrated.

To show significant clinical benefit,currently atleast ≥ 8 patients will have to achieve CBR at 24weeks.But if number of patients enrolled in study is higher than the planned number of 33 patients (approximately 44 to 46), then the requirement for number of patients to have achieved CBR will also increase (upto >= 10 patients).

CBR will be summarized by frequency and percentage together with the 95% confidence intervals. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper & Pearson, 1934].

CBR will be calculated based on FAS; however, patients with only non-measurable disease at baseline will be included in the numerator if they achieved a complete response.

For primary efficacy variable, the analysis time point is when all patients who are enrolled complete 24 weeks or discontinue from the study earlier. Phase 1 patients who had received the RP2D and are post CDK 4/6 completing 24 weeks or discontinue early will also be included in the final phase II analysis.

When examining clinical benefit, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for CBR calculation.

For the primary analysis, CBR will be assessed based on the centrally assessed tumor responses provided by the Investigator according to RECIST Version 1.1. Additionally, above analysis will be repeated for CBR based on the locally assessed tumor response using full analysis set. Analysis will also be performed using per protocol analysis set, as appropriate.

3.5.3 Handling of missing values/censoring/discontinuations

Not Applicable.

3.5.4 Supportive analyses

Not Applicable.

3.6 Analysis of the key secondary objective

Not Applicable

3.7 Analysis of secondary efficacy objective(s)

- **Phase I**

The secondary objectives for the Phase I, dose escalation part of this study are:

- To determine the safety and tolerability based on NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 when treated with ribociclib + everolimus + exemestane continuously in subjects with HR+, HER2 negative advanced breast cancer.
- To determine the pharmacokinetic (PK) profile of everolimus and ribociclib when dosed continuously in the triplet combination.
- To assess the preliminary anti-tumor activity of the triplet combination of ribociclib + everolimus + exemestane when combination is given continuously.

- **Phase II**

The secondary objectives for the Phase II part of this trial are:

- To determine centrally assessed Progression Free Survival (PFS)
- To determine Overall Response Rate (ORR)
- To determine Overall Survival (OS)
- To determine Duration of Overall Response (DOR)
- To evaluate time to deterioration or ECOG performance status
- To determine safety and tolerability
- To determine the PK profile of ribociclib and everolimus in the triplet combination

3.7.1 Secondary end points

- **Phase I**

The secondary end points for the study are:

- Incidence and severity of adverse events (AE) and serious adverse events (SAE), clinical laboratory values, vital signs and electrocardiogram (ECGs), dose interruptions, reductions and dose intensity.
- PK parameters including, but not limited to, $AUC_{(0-4)}$, C_{trough}, C_{max}, accumulation ratio (Racc).
- Progression Free Survival (PFS), Overall response rate (ORR), Disease Control Rate (DCR), Clinical benefit rate (CBR) based on the responses provided by the Investigator on locally assessed data per RECIST v1.1.

ORR, DCR and CBR will be assessed based on the responses provided by the Investigator on centrally and locally assessed data.

- **Phase II**

The secondary end points for the Phase II part of this trial, are:

- PFS
- ORR
- OS
- DOR
- Time to definitive deterioration of ECOG performance status from baseline.
- Adverse Events (AEs), serious AE (SAEs), changes in hematology and chemistry values, vital signs, dose interruptions, reductions and dose intensity.
- PK parameters including, but not limited to, $AUC_{(0-4)}$, C_{trough}, C_{max}, accumulation ratio (R_{acc}).

ORR, DOR, and PFS will be assessed based on the responses provided by the Investigator on centrally and locally assessed data.

3.7.2 Statistical hypothesis, model, and method of analysis

- **Phase I**

3.7.2.1 ORR, DCR and CBR

- ORR:

Overall response rate (ORR) defined as the proportion of patients who's best overall response is either complete response (CR) or partial response (PR) according to RECIST 1.1. ORR will be calculated based on FAS; however, patients with only non-measurable disease at baseline will be included in the numerator if they achieved a complete response. ORR will be summarized by frequency and percentage. The exact 95% two-sided confidence interval will also be provided.

When examining overall response, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR calculation.

Best overall response for each patient will be listed and summarized on FAS.

- DCR:

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. DCR will be calculated based on FAS; however, patients with only non-measurable disease at baseline will be included in the numerator if they achieved a complete response. DCR will be summarized by frequency and percentage. The exact 95% two-sided confidence interval will also be provided.

When examining disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for DCR calculation.

- CBR:

CBR is defined as the proportion of patients with a CR, PR, SD or NCRNPD as per RECIST V1.1 by week 24. Thus, any instance of CR, PR, SD or NCRNPD in the first 24 weeks of the treatment, without having an instance of PD will be accounted for, while calculating CBR. The instances of unconfirmed CR and/or PR will also be accounted for, while calculating CBR.

CBR will be calculated based on FAS; however, patients with only non-measurable disease at baseline will be included in the numerator if they achieved a complete response. CBR will be summarized by frequency and percentage together with the 95% confidence intervals. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper & Pearson, 1934].

When examining clinical benefit, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for CBR calculation.

- **Phase II**

3.7.2.2 PFS, ORR, OS and DOR

- PFS:

Progression-free survival (PFS) is defined as the time from date of treatment to the date of first documented progression or death due to any cause. For PFS, a patient who didn't have the event at the date the analysis data cut-off will be censored at the time of the last adequate assessment, prior to data cut-off. PFS will be assessed based on the responses provided by the Investigator on centrally assessed data. The PFS will be analyzed using FAS.

PFS will be analyzed using the Kaplan-Meier Product-Limit method. Estimates of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, if applicable. Additionally, above analysis will be repeated on the locally assessed tumor response. Analysis will also be performed using per protocol analysis set, as appropriate.

- ORR:

Overall response rate (ORR) defined as the proportion of patients who's best overall response is either complete response (CR) or partial response (PR) according to RECIST 1.1. ORR will be calculated based on FAS; however, patients with only non-measurable disease at baseline will be included in the numerator if they achieved a complete response. ORR will be summarized by frequency and percentage. The exact 95% two-sided confidence interval will also be provided.

When examining overall response, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR calculation.

Best overall response for each patient will be listed and summarized on FAS.

- OS:

Overall survival (OS) is defined as the time from date of first treatment to the date of death due to any cause. If a patient is not known to have died, survival will be censored at the last date of contact.

OS will also be summarized by Kaplan-Meier Product-Limit method based on FAS. Estimates of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, if applicable.

- DOR:

Duration of Overall Response (DOR) applies only to patients whose best overall response is CR or PR according to RECIST 1.1. The start date is the date of first documented response (CR or PR) and the end date is the date defined as first documented progression or death due to underlying cancer. In other words, the start date should be determined using the time that the response was first determined and not using the time the response was confirmed. If a patient had not had an event, duration will be censored at the date of the last adequate tumor assessment. DOR will be listed and summarized based on FAS.

DOR will also be summarized by Kaplan-Meier Product-Limit method based on FAS. Estimates of the 25^{th}, median and 75^{th} percentile of the DOR and their 95% confidence intervals will be provided, if applicable.

In addition of above endpoints waterfall plot and swimmer plot will also be presented. The waterfall plot displays the best percentage change from baseline in the sum of the longest diameter of all target lesions for each patient by dose cohort of phase I and by group of phase Viand swimmer plot displays patient's tumor response status with length of treatment duration.

Additionally, the concordance in best response according RECIST1.1 per central review and local evaluation will be summarized. Kappa coefficients were calculated to characterize the agreement in response assessments between local evaluation and central review (kappa = 1 implies perfect agreement).

3.7.2.3 Safety and Tolerability

Please refer to the Section 3.8 for Safety analysis details.

3.7.2.4 PK profile of ribociclib and everolimus

Please refer to the Section 3.9 for details on PK analysis for ribociclib and everolimus.

3.7.2.5 Definitive deterioration of the ECOG PS:

ECOG performance scale will be used to assess physical health of patients.

An analysis of the time to definitive deterioration of the ECOG PS by one category of the score from the date of first treatment will be performed. Baseline is the last available assessment on or before date of first treatment. Definitive deterioration is defined as an increase in ECOG PS by at least one category from the baseline score or death due to any cause. Deterioration is considered definitive if no improvements in the ECOG PS status is observed at a subsequent time of measurement during the treatment period following the time point where the deterioration is observed. (Example 1: if the score is 1 at baseline and then 1 , 2 , 1 , 2 , 3 at study days 28 , 57 , 83 , 115 , 150, respectively, then the time to definitive deterioration is 115 days, Example 2: if the score is 1 at baseline and then 1 , 1 , 2 at study days 28 , 57 , 83, respectively, with no assessment of the ECOG PS status after day 83 then the time to definitive deterioration is 83 days).

If a definitive deterioration is observed after $\geq$ 2 missing assessments, this event will be censored at the date of the last ECOG PS assessment prior to the deterioration. Patients that have not worsened will be censored at the date of last available assessment

Time to Definitive Deterioration (TDD) will be summarized by Kaplan-Meier Product-Limit method based on FAS. Estimates of the 25th, median and 75th percentile and their 95% confidence intervals will be provided, if applicable.

Additionally, ECOG PS data will be summarized at each scheduled assessment time point.

The following time based intervals will be used to group the ECOG PS data over time.

Table 2-6 Time window for ECOG assessment

	Time Interval
Baseline	Day 1 (if Day 1 data is missing then use the screening)

Cycle 2 Day 1	Day 2 to day 42 (2nd assessment)
Cycle 3 Day 1	Day 43 to day 70 (3rd assessment)
Cycle 4, 5,… until end of treatment	+/- 2 weeks centered around the planned assessment date: i.e. days 71 to 98 for Day 1 of cycle 4 (4th assessment) days 99 to 126 for Day 1 of cycle 5 (5th assessment) days [(k-1)*28-14; (k-1)*28+13] for Day 1 of cycle k (k+1th assessment)
End of Treatment	Assessment taken at the end of treatment visit

3.7.2.6 Safety and Tolerability

Please refer to the Section 3.8 for Safety analysis details.

3.7.2.7 PK profile of ribociclib and everolimus

Please refer to the Section 3.9 for details on PK analysis for ribociclib and everolimus.

3.7.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed in any manner.

3.8 Safety analyses

For all safety analyses, the safety analysis set will be used. All safety data will be listed and tables will be summarized by dose cohorts of Phase I and overall for Phase II.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication

2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication

3. post-treatment period: starting at day 30+1 after last dose of study medication.

3.8.1 Adverse events (AEs)

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though the Study Evaluation Completion page. Adverse events will be coded using the most recent version of the medical dictionary for regulatory activities (MedDRA) available at the time of each analysis.

The AEs experienced by the patients in all the observation periods will be listed. The AEs reported in pre-treatment and post-treatment period will be flagged in the listing. In an AE listing, details will be provided for severity grade of AE, seriousness of AE, its relationship to

study treatment, its duration, action taken, outcome, and whether medication or therapy was given to patient.

Treatment Emergent AEs are those, which start in on-treatment period, or which start in pre-treatment period but worsen in on-treatment period. Summary tables for all TEAEs will be provided by study treatment group.

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. The tables will be summarized alphabetically by SOC and in decreasing frequency of PTs. The decreasing order of PTs will be based on the total count.

AE overview table will be provided with information on number and percentage of patients having any AE, any SAE, any Severe AE, any AE leading to discontinuation of study drug, dose adjustments and interruption, any fatal AE and deaths due to any cause. The incidences of all TEAEs will be summarized by the SOC and PT. In addition to this, the incidences of all grades of TEAE and of grades 3 and 4 TEAE will be summarized. Serious TEAEs including fatal and non-fatal AEs, Severe TEAEs, AEs with relationship to study treatment, AEs leading to discontinuation of any study treatment, AEs leading to dose adjustment or interruption, will also be summarized. All AEs will be summarized regardless of relationship to study treatment.

3.8.1.1 Adverse events of special interest / grouping of AEs

Not Applicable

3.8.2 Deaths

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

3.8.3 Laboratory data

The grading of the laboratory data will be done using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For laboratory tests, the study's bio statistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a 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 graded by the low/normal/high classifications based on laboratory normal ranges.

If there are multiple post-baseline evaluations within each visit, the second unscheduled measurement will be summarized. If there is only one unscheduled measurement, then the unscheduled measurement will be used for reporting.

If the lower limits of normal ranges used in CTCAE definitions are missing, then they have to be replaced by a clinical meaningful limit.

The results will be listed separately for hematology, biochemistry and urinalysis laboratory tests, along with details on the CTCAE grades and/or classifications relative to laboratory normal ranges.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests, by dose cohorts of Phase I and by group of Phase II:

- Change from baseline to worst value by dose groups (descriptive statistics)
- Shift table from baseline to maximum value on-treatment value, for those lab tests having CTCAE grades (frequency count and percentages)
- Shift table from baseline to worst on-treatment value, for those lab tests not having CTCAE grades, based on the low/normal/high classification (frequency count and percentages)
- Table for newly occurring on-treatment grades 3 or 4 (frequency count and percentages)
- Number and percentage of patients with notable hepatic laboratory values by regimen and treatment group. Please note that notable hepatic laboratory values are defined as:
    - ALT or AST > 3xULN, > 5xULN, > 8xULN, > 10xULN, > 20xULN
    - TBIL > 1.0x ULN and <= 2.0x ULN, TBIL > 2.0x ULN
    - ALP > 1.5 xULN
    - ALP>2.0xULN
    - ALT or AST > 3.0x ULN and TBIL > 2.0x ULN and ALP<2.0x ULN at any time during the trial enrollment and not necessarily concomitant

Listing of all laboratory data with values flagged to show the corresponding CTCAE Grades and the classifications relative to the laboratory normal ranges.

3.8.4 Other safety data

3.8.4.1 ECG and cardiac imaging data

3.8.4.1.1 ECG data

12-lead ECGs including PR, QRS, QT, QTcF, and HR intervals will be obtained for each subject during the study. All ECG data will be listed, notable values will be flagged and any other information collected will be listed as appropriate. Triplicate ECGs, performed in case when QTcF prolongation of >= 480 msec is observed, will also be listed.

The following summaries will be provided by dose cohorts of Phase I and overall for Phase II:

- Change from baseline in QT intervals for each visit.
- The frequency and percentage of patients with notable ECGs and newly occurring qualitative ECG abnormalities.

Listing of ECG intervals will be provided, where ECG notable parameters will be flagged. Listing of ECG findings, cardiac imaging and QT prolonging concomitant medication will also be produced.

The overall assessment results will be summarized using frequency and percentages, for shifts from baseline to worst ECG value on treatment.

The number and percentage of subjects with notable ECG values will be presented by dose group. Notable abnormal values for ECG parameter will be listed and flagged.

QT, or 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 > 200 ms

QRS

- Increase from baseline >25% and to a value > 110 ms
- New values of QRS > 110 ms

3.8.4.1.2 Cardiac Imaging Data

Cardiac imaging results from MUGA Scan or ECHO, collected at screening will also be listed.

3.8.4.2 Vital signs

The vital sign parameters, sitting blood pressure, sitting pulse, respiratory rate, weight, height, BMI and body temperature, will be listed for each visit. Notable abnormal values will be flagged.

The vital sign value results will be summarized by dose cohort of Phase I and by group of Phase II as mentioned below:

- Change from baseline to worst value (descriptive statistics)
- Shift table from baseline to maximum value on-treatment value, for all vital sign parameters (frequency count and percentages)
- Clinically notable vital sign abnormalities (frequency count and percentages)

Notable abnormalities for vital sign values is as follows:

Table 3-7 Clinically notable elevated values

Variable	Criteria
Systolic BP	≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
Diastolic BP	≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
Body temperature	≥ 39.1°C (102.3°F)
Weight	increase from baseline of ≥ 10%
Heart rate	≥ 120 bpm with increase from baseline of ≥ 15 bpm

Table 3-8 Clinically notable below normal values

Variable	Criteria
Systolic BP	≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
Diastolic BP	≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
Body temperature	≤ 35°C (95°F)
Weight	decrease from baseline of ≥ 10%
Heart rate	< 50 bpm with decrease from baseline of ≥15 bpm

3.8.4.3 Pregnancy Test

Pregnancy test results in serum and urine will be listed.

3.8.4.4 Physical Examination

The results of Physical examination at screening will be listed.

3.8.4.5 Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number of treatment dose interruptions and dose change. Reasons for dose interruption and dose change will be listed by patient and summarized for Safety set, and will be presented by dose cohorts of Phase I by group of Phase II.

Cumulative dose, dose intensity and relative dose intensity of ribociclib, everolimus and exemestane will be listed by patient and summarized.

Categories for relative dose intensity for ribociclib, everolimus and exemestane will be specified as follows:

- <0.7
- ≥0.7 - <0.9

- ≥0.9

The number and proportion of patients within each category will be presented.

3.9 Pharmacokinetic end points

Ribociclib and everolimus concentrations will be listed and summarized descriptively based on planned timepoints. The concentration data will be provided for all patients in PK analysis set.

Descriptive statistics will include mean, standard deviation, CV%, median, range. All PK parameters will be provided by dose group and study day. When a geometric mean is presented, it will be stated as such. Only median values and ranges will be given for T_{max}.

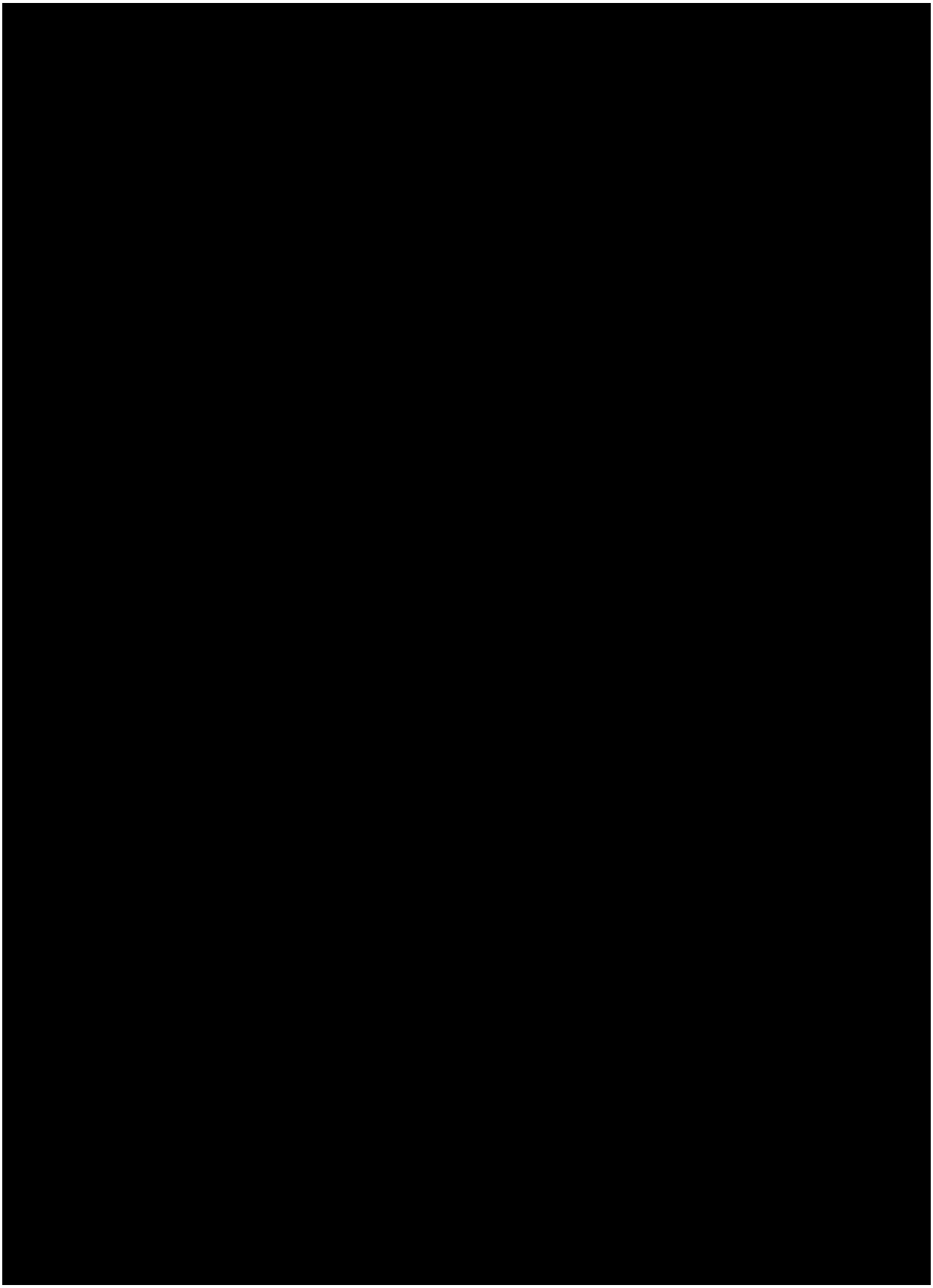
Descriptive graphical plots of individual plasma concentration by time will be generated for ribociclib (and LEQ803) and everolimus. Also mean concentration-time profiles will be generated for ribociclib (and LEQ803) and everolimus.

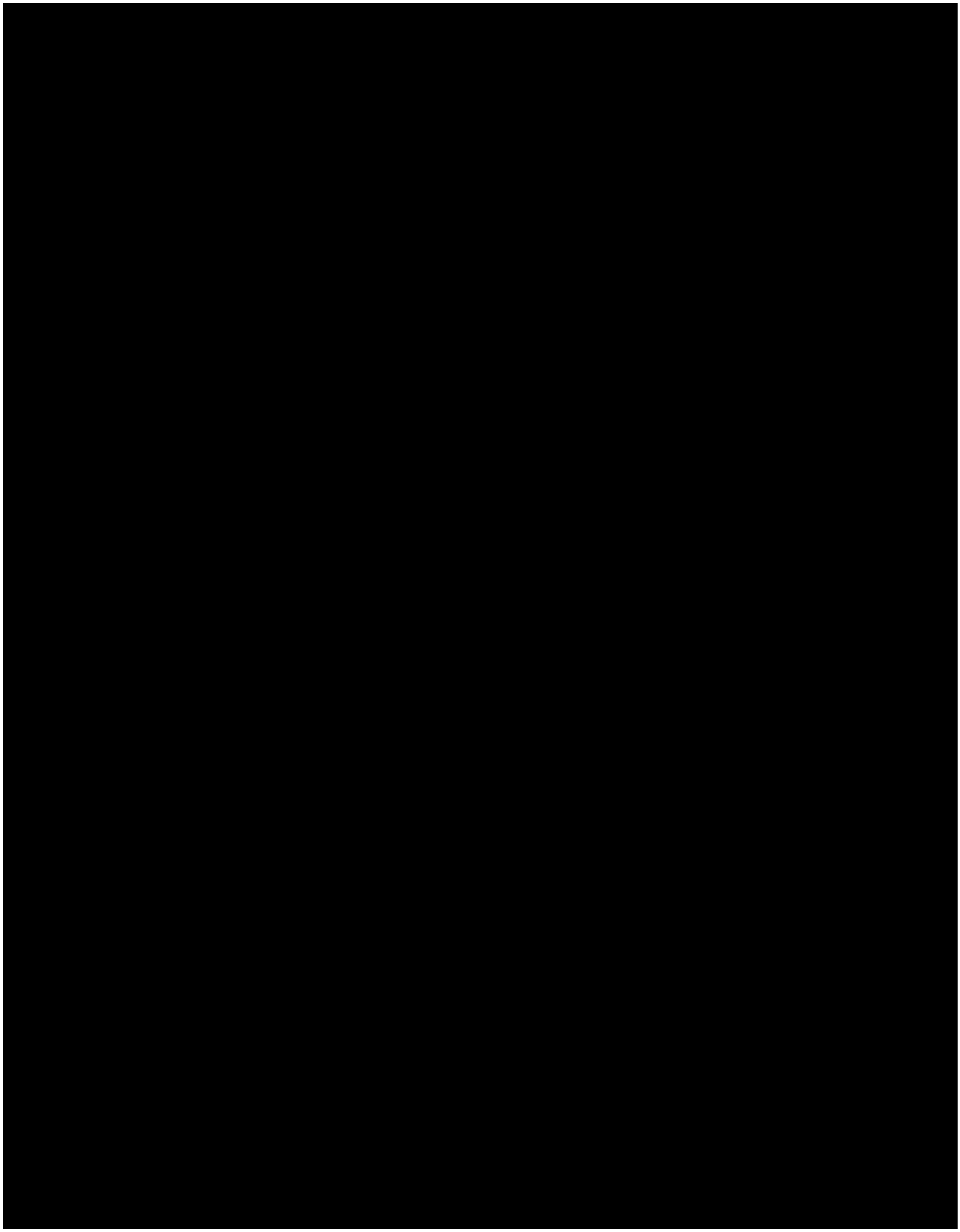
3.10 PD and PK/PD analyses

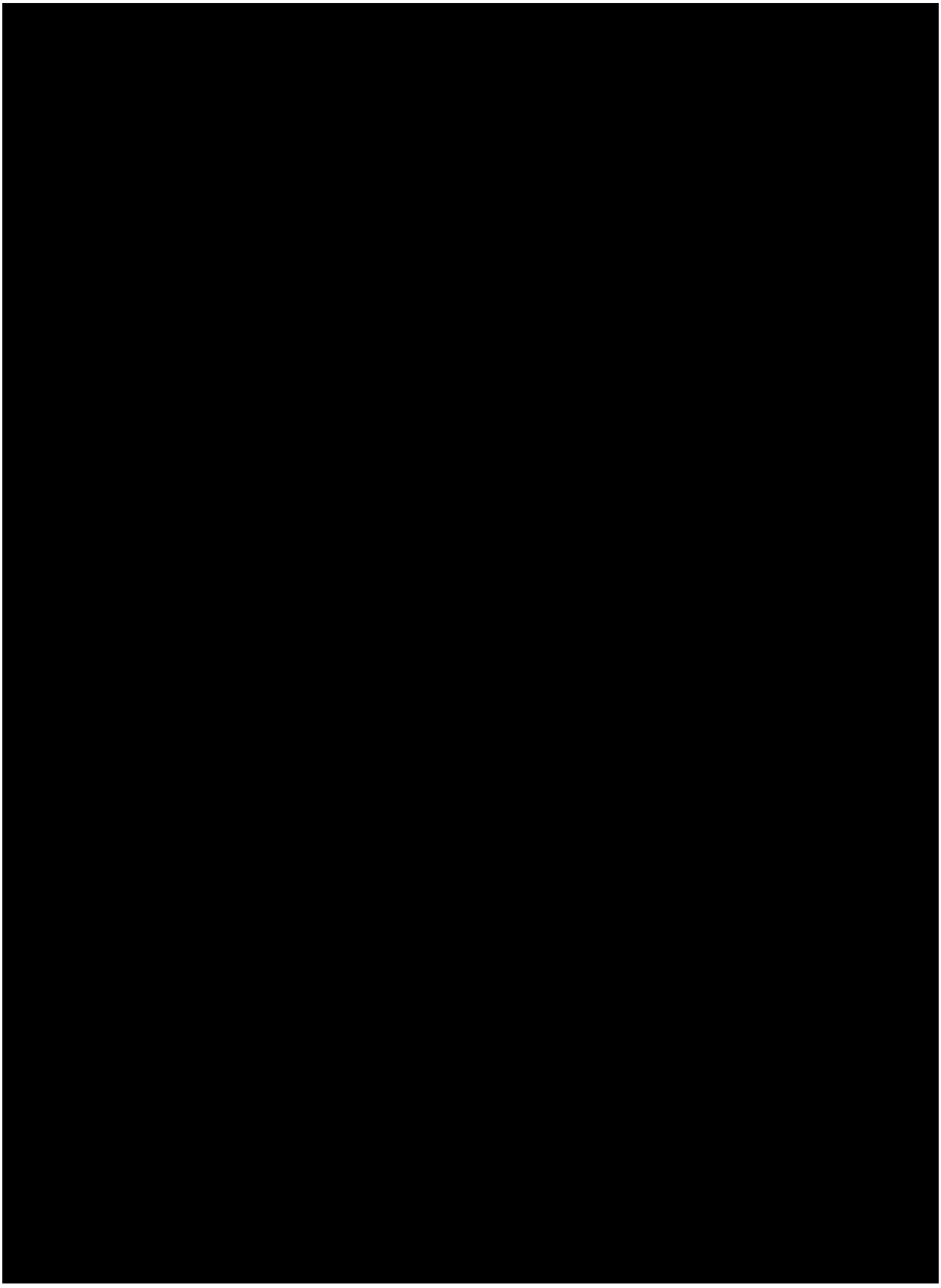
Not Applicable

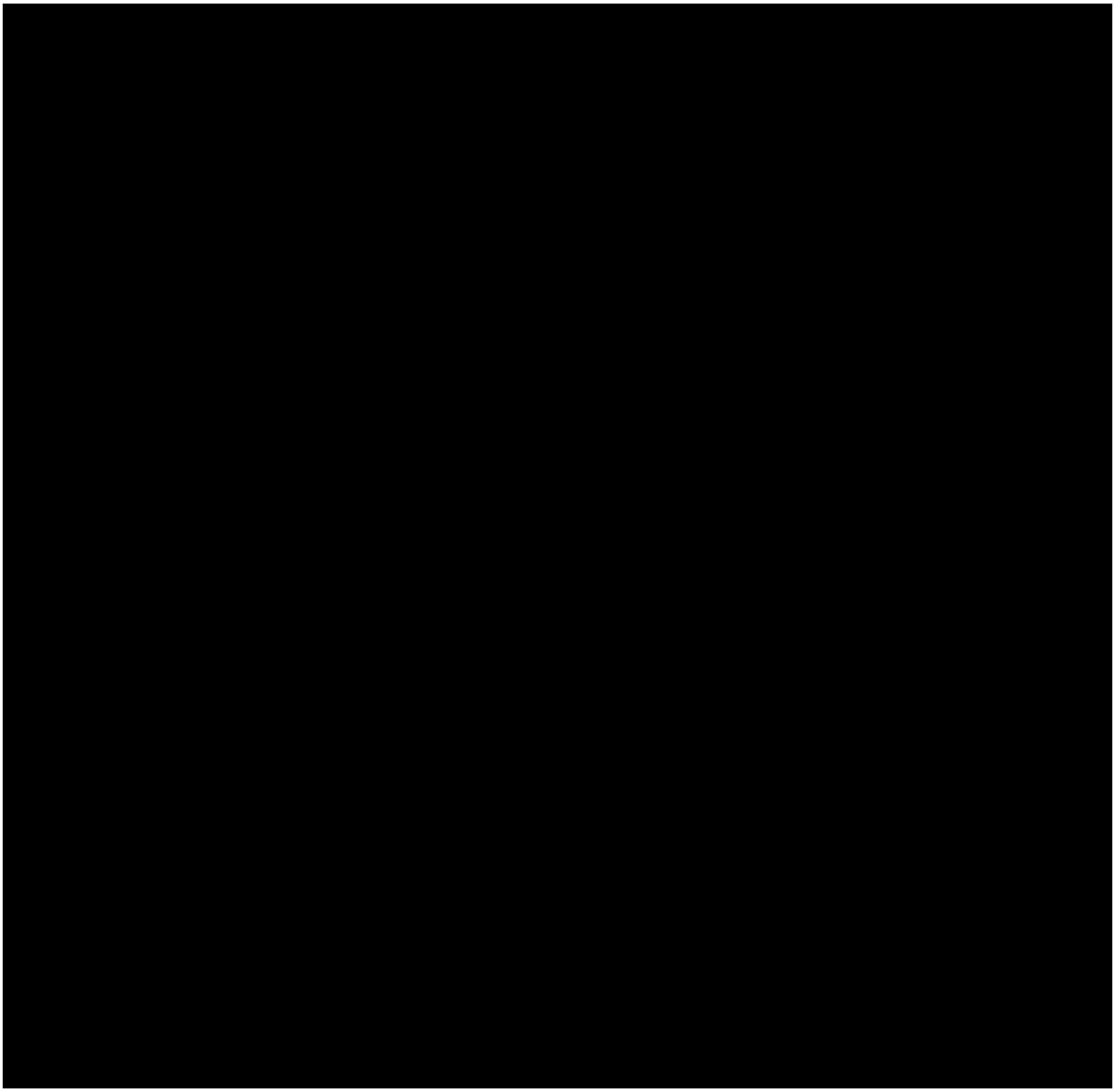
3.11 Patient-reported outcomes

Not Applicable









3.15 Interim analysis

No formal interim analysis is planned One interim statistical analysis will be done after completing Phase I part of the study. The final analysis will be after completing Phase II of the study.

4 Sample size calculation

Phase I: In the phase I of the study, there will be 3-6 patients per dose level cohort (for a total of 3 cohorts). A RP2D will be based on safety profile of the dose escalation (cohort A&B) and the dose de-escalation (cohort C). RP2D will be defined as the optimal dose level at which 33%

or less experience DLTs. Thus, including confirmation, at least 3-6 patients will be required for Phase I for each cohort.

Phase II: The sample size is based on an exact test for single proportion to test the null hypothesis H0: $p \leq 0.10$ where p is the clinical benefit rate in 24 weeks. If the true rate is $p \geq 30\%$, then with one-sided alpha level of 0.05% and a power of 80%, a minimum of approximately 60 (30 per group) evaluable patients are required for the study.

Including dropout rate of 10%, to get 60 evaluable patients, a total of approximately 66 patients (33 patients per group) will be enrolled for the phase 2 of the study for each group (group 1 and group 2). Thus, if fewer than 8 patients show clinical benefit at 24 weeks out of 33 patients within each group then the study will not show significant clinical benefit. Thus, approximately at least 66 patients (33 patients per group (group 1&2)) will be required to be enrolled for the Phase II of the study.

So far 46 patients for group 1 and 33 patients for group 2 are recruited for phase 2.

5 Change to protocol specified analyses

None

6 Appendix

6.1 Imputation rules

6.1.1 Study drug

In the calculation of treatment exposure duration, if a dosing record has either a missing end date (for the last record for that treatment component) or an end date after the cut-off date, the cut-off date will be used as the end date. Such imputed data will be flagged in the listings. Where a date is recorded as a partial date, the missing day will be imputed as follows:

Start date: The day will be imputed by the 15th of the month. If day and month are missing day and month will be imputed by July 1st of the year. If there is a record indicating that the dose record started earlier, the start date will be imputed by the end date of the previous record + 1 day. In case the imputed start date is later than the complete end date, the record will not be considered for analysis.

End date: The day will be imputed by the 15th of the month, and if day and month are missing then by July 1st of the year. If there is a record indicating that this started later, the end date will be imputed by the start date of the next record - 1 day. In case the imputed end date is earlier than the complete start date, the record will not be considered for analysis.

Imputed DAR start and end dates will be flagged in the listings.

The protocol allows for continuous dosing record entry with start dates and end dates for all compounds of study treatment. A separate dosing record should be entered whenever there is a

change in the dosing which can be due to dose change, delay or missed doses. If the start date and end date is on the same date then that DAR record will be called single dose DAR record.

For dates known to be within the trial period, the last known contact date will be used if this imputation makes the date later than the last known contact date but within the trial completion date. If the imputed date is earlier than the first medication date, the first medication date will be used.

For dates prior to the treatment start, the treatment start date will be used if this imputation makes the date later than the treatment start date.

6.1.2 AE date imputation

6.1.2.1 AE Start Date Imputation

If the adverse event start date was entirely missing or patient has not yet started study treatment no imputation was done.

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year is available and the year is less than year of the treatment start date, the AE started before treatment. Therefore:
    a. If the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid year point (01JulYYYY).
    b. Else if the AE year is less than the treatment year and the AE month is not missing, the imputed AE start date is set to the mid month point (15MONYYYY).
3. If the AE start date year is available and value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid month point (15MONYYYY).
    c. Else if the AE month is greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

The table below presents the algorithm used to impute the partial AE start date:

	MON MISSING	**MON < TRT_MON**	**MON = TRT_MON**	**MON > TRT_MON**
YYYY MISSING	_null_	_null_	_null	_null_
YYYY < TRT_YR	01JULYYYY	15MONYYYY	15MONYYYY	15MONYYYY
YYYY = TRT_YR	TRTSTD+1	15MONYYYY	MAX(01MONYYYY, TRTSTD+1)	MAX(01MONYYYY, TRTSTD+1)
YYYY > TRT_YR	01JANYYYY	MAX(01MONYYYY, TRTSTD+1)	MAX(01MONYYYY, TRTSTD+1)	MAX(01MONYYYY, TRTSTD+1)

Where:

MON = Month of Partial Adverse Event Start Date

AE_YR =Year of Partial Adverse Event Start Date

TRT_MON= Month of Treatment Start Date

TRT_YR= Year of Treatment Start Date

TRTSTD = Treatment Start Date

6.1.2.2 AE End Date Imputation

Rules for imputing the AE end date:

- Rules for imputing the AE end date:
- If AE day is missing but year and month are available, then the AE end date is set to minimum of (end date of follow-up period (treatment end date + 30 days), last day of the month, date of death, cutoff date).
- If AE month and day are missing but year is available, then it is set to minimum of (end date of follow-up period, Dec-31 of the year, date of death, cutoff date).
- If AE year is missing the end date will not be imputed.
- If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date. If patient has not yet started study treatment, no imputation will be done for AE end date.

6.1.3 Concomitant medication date imputation

6.1.3.1 Concomitant medication start date imputation

Rules for imputing the CMD start date:

1. If the CMD start date year value is missing, the imputed CMD start date is set to one day prior to the date of first dose.
2. If the CMD start date year value is less than the treatment start date year value, the CMD started before the treatment. Therefore:
    a) If the CMD month is missing, the imputed CMD start date is set to the mid-year point (01JulYYYY).
    b) Else if the CMD month is not missing, the imputed CMD start date is set to the mid-month point (15MONYYYY).
3. If the CMD start date year value is greater than the treatment start date year value, the CMD started after the treatment. Therefore:
    a) If the CMD month is missing, the imputed CMD start date is set to the year start point (01JanYYYY).

Else if the CMD month is not missing, the imputed CMD start date is set to the month start point (01MONYYYY).

1. If the CMD start date year value is equal to the treatment start date year value:
    a) And the CMD month is missing or the CMD month is equal to treatment start month, then the imputed CMD start date is set to one day after the treatment start date.
    b) Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to the mid-month point (15MONYYYY).
    c) Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to the start month point (01MONYYYY).

6.1.3.2 Concomitant medication end date imputation

Rules for imputing the CMD end date (including on-going records CM.CMONGO='Y'):

- If CMD end day is missing and CMD month/year are non-missing:
    a) If day is missing but month/year are not missing impute day with the last day of the month.
- If CMD end day/month are missing and CMD year is non-missing:
    a) If CMD year is prior to or greater than the year of first dose of treatment, assume the 31 Dec.
    b) Else if CMD year is equal to the year of first dose of treatment, the imputed end date is the min of (treatment end date, 31st of December).
- If imputed CMD end date is less than the CMD start date, use the CMD end date as the imputed CMD start date.
- If imputed CMD end date is greater than date of death, date of cutoff, or end date of follow-up period, then the imputed CMD end date will take the minimal date among date of death, date of cutoff, or end date of follow-up period.

6.1.3.3 Prior therapies date imputation

Not Applicable

6.1.3.4 Post therapies date imputation

Not Applicable

6.1.3.5 Other imputations

Not Applicable

6.2 AEs coding/grading

Adverse events will be coded using the Medical Dictionary For Regulatory Activities (MedDRA) version 19.1 or higher.

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

6.3 Laboratory parameters derivations

6.3.1 Differential Counts:

CTCAE grading is based on absolute values. However, for some labs this data may not present itself as absolute counts and be recorded as percentage or fraction in the database (e.g. neutrophils).

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)

6.4 Statistical models

6.4.1 Analysis of Response Rate

Patients with clinical benefit, disease control and responders are summarized in terms of percentage rate with 95% confidence interval. An exact binomial confidence interval (implemented using the SAS procedure FREQ with the EXACT statement for one-way tables) is calculated (Clopper & Pearson, 1934).

The SAS procedure FREQ was used with the following code:

PROC FREQ DATA=*dataset*;

BY *treatment*;

TABLES *response* / binomial;

EXACT binomial;

RUN;

6.4.2 Time to event analysis

For analyzing PFS, OS and DOR, TDD, PROC LIFETEST SAS® procedure will be used for Kaplan Meier plots for each dose group. Median PFS and Median OS, Median TDD for each dose group will be obtained along with 95% confidence intervals calculated by SAS procedure LIFETEST using method of Brookmeyer and Crowley (1982).

The following variables will be used:

- Progression, Survival, Definitive deterioration: Event
- Censoring indicator variable: 1=Censored; 0=Event

6.5 Rule of exclusion criteria of analysis sets

Not Applicable

7 Reference

1. RECIST Guidelines version 1.1 - Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)
2. *Health-Related Quality of Life of Patients With Advanced Breast Cancer Treated With Everolimus Plus Exemestane Versus Placebo Plus Exemestane in the Phase 3, Randomized, Controlled, BOLERO-2 Trial* - Howard A. Burris, III, MD; Fabienne Lebrun, MD; Hope S. Rugo, MD; J. Thaddeus Beck, MD; Martine Piccart, MD, PhD; Patrick Neven, MD, PhD; Jose Baselga, MD, PhD; Katarina Petrakova, PhD; Gabriel N. Hortobagyi, MD; Anna Komorowski, MD; Edmond Chouinard, MD; Robyn Young, MD; Michael Gnant, MD; Kathleen I. Pritchard, MD; Lee Bennett, MS; Jean-Francois Ricci, PhD; Hounayda Bauly, PhD; Tetiana Taran, MD; Tarek Sahmoud, MD, PhD; and Shinzaburo Noguchi, MD
3. *Safety and Efficacy of RAD001 (Everolimus) Monotherapy Plus Best Supportive Care in Patients With Advanced Gastric Cancer (AGC) (GRANITE-1)* - https://clinicaltrials.gov/ct2/show/results/NCT00879333?sect=Xa0156#outcome4
4. *Everolimus Plus Exemestane in Postmenopausal Patients with HR$^+$ Breast Cancer: BOLERO-2 Final Progression-Free Survival Analysis* http://link.springer.com/article/10.1007/s12325-013-0060-1
5. *Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time, Biometrics 38, 29 - 41.*
6. *Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413.*