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LEE011/ribociclib

Clinical Trial Protocol CLEE011A3201C / NCT03839823

A phase II randomized study of the combination of Ribociclib plus goserelin acetate with Hormonal Therapy versus physician choice chemotherapy in premenopausal or perimenopausal patients with hormone receptor-positive/HER2-negative inoperable locally advanced or metastatic breast cancer - RIGHT Choice Study

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List of abbreviations

ABC	Advanced Breast Cancer
AE	Adverse Event
AESI	Adverse events of special interest
AIs	Aromatase inhibitors
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
b.i.d.	bis in die/twice a day
BMI	Body Mass Index
BOR	Best overall response
BSA	Body Surface Area
BSEP	Bile salt export pump
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit rate
CDKs	Cyclin-dependent serine-threonine protein kinases
CDP	Clinical Development Plan
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
COA	Clinical Outcome Assessment
CQA	Clinical Quality Assurance
CR	Complete Response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTC	Common Terminology Criteria
CV	coefficient of variation
DFS	Disease Free Survival
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EOT	End of Treatment
ER	Estrogen Receptor
ESMO-MCBS	The European Society for Medical Oncology - Magnitude of Clinical Benefit Grading Scale
FAS	Full Analysis Set
FFPE	Formalin-Fixed Paraffin-Embedded
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GCSF	Granulocyte-colony stimulating factor
H	Hour
HER2	Human Epidermal Growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard Ratio
HR+	Human Receptor Positive
IB	Investigator’s Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat
IV	intravenous
LDH	lactate dehydrogenase
LFT	Liver function test
LHRH	Luteinizing Hormone-Releasing Hormone
MBC	Metastatic Breast Cancer
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
ml	milliliter(s)
OFS	Ovarian Function Suppression
ORR	Overall Response Rate
OS	Overall Survival
p.o.	oral(ly)
PET	Positron Emission Tomography
PFS	Progression Free Survival
PgR	Progesterone receptor
PK	Pharmacokinetics
PLD	Pegylated liposomal doxorubicin
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Prothrombin Time
Q.D.	once a day
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RAP/SAP	Report and Analysis Plan/ Statistical Analysis Plan
RBC	red blood cell(s)
RECIST	Response Evaluation Criteria In Solid Tumors
[redacted]	[redacted]
s.c.	subcutaneous
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
TBIL	Total bilirubin
TdP	Torsades de Pointes
TTF	Time to treatment failure
TTR	Time to response
WBC	White blood cell(s)
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.

Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures.
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Protocol summary

Protocol number	CLEE011A3201C
Full Title	A phase II randomized study of the combination of Ribociclib plus goserelin acetate with Hormonal Therapy versus physician choice chemotherapy in premenopausal or perimenopausal patients with hormone receptor-positive/HER2-negative inoperable locally advanced or metastatic breast cancer – RIGHT Choice Study
Brief title	Comparing the combination of Ribociclib plus goserelin acetate with hormonal therapy versus combination chemotherapy in premenopausal or perimenopausal patients with advanced or metastatic breast cancer
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Recent phase III clinical trials demonstrated that CDK4/6 inhibitor plus endocrine therapy could generate a tumor response rate higher than 50% (in measurable lesions), which is higher than what has been reported by most of the chemotherapy regimens in phase III studies. The purpose of this trial is to compare the two treatment modalities in the patients with aggressive disease in HR+/HER2- metastatic pre/peri-menopausal breast cancer setting.
Primary Objective(s)	The primary objective of this study is to determine whether treatment with NSAI + goserelin+ ribociclib prolongs PFS compared to treatment with combination chemotherapy in premenopausal or perimenopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer.
Secondary Objectives	The secondary objectives are listed below: • To compare time to treatment failure (TTF) between the two treatment arms. • To compare 3-month treatment failure rate between the two treatment arms • To determine whether treatment with NSAI + goserelin + ribociclib increases overall response rate (ORR), clinical benefit rate (CBR), and Time to response (TTR) compared to treatment with combination chemotherapy. • To compare the overall survival (OS) between two treatment arms. • To evaluate the safety of ribociclib in combination with NSAI and goserelin, and combination chemotherapies. • To compare patient reported outcomes for health-related quality of life in the two treatment arms.
[redacted]	
Study design	This is a randomized, phase II, open label, multi-center trial comparing the combination of NSAI (letrozole or anastrozole) + goserelin + ribociclib

	versus combination chemotherapy (either of docetaxel + capecitabine, paclitaxel + gemcitabine or capecitabine + vinorelbine). Premenopausal or perimenopausal women with HR positive, HER2-negative, advanced breast cancer with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and having symptomatic visceral metastases, or rapid progression of disease or impending visceral compromise, or markedly symptomatic non visceral disease will be considered for this study. An end of treatment (EOT) visit will be performed either at disease progression (radiologically documented according to RECIST 1.1 criteria), unacceptable toxicity, death, or discontinuation from the study treatment for any other reason, including consent withdrawal, patient is lost to follow-up, or the sponsor terminates the study (whichever occurs first) and all the end of treatment procedures will be completed. End of study will be after at least 46 months from first patient first visit (FPFV) or when required number of OS events have been reached (80% of 222 patients have died), whichever occurs first.
Population	The study will include approximately 222, adult premenopausal or perimenopausal women with ECOG status 0 - 2, HR positive, HER2-negative, advanced breast cancer and have not received neither prior hormonal therapy nor chemotherapies in advanced breast cancer setting. To be considered for this study, the patients must have an advanced disease status that need combination chemotherapy according to PI's judgment.
Key Inclusion criteria	Following are the key inclusion criteria; please refer to Section 5.1 for details on and full listing of inclusion criteria. 1. Patient is an adult female ≥ 18 years old and < 60 years old at the time of informed consent. Written informed consent must be obtained prior to any screening procedures 2. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer based on the most recently analyzed tissue sample and all tested by local laboratory. ER should be more than 10% ER positive or Allred ≥5 by local laboratory testing. 3. Patient has HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing and based on the most recently analyzed tissue sample. 4. Women with inoperable locally advanced or metastatic breast cancer not amenable to curative therapy. Patients must fulfill at least one of the following criteria to be considered that combination chemotherapy is needed according to PI's judgment. However, for patients who are eligible under inoperable locally advanced breast cancer or criteria 4c, the recruitment is stopped to enrich patient population with visceral metastases. a Symptomatic visceral metastases b Rapid progression of disease or impending visceral compromise. c Markedly symptomatic non visceral disease if the treating physician opts to give chemotherapy for rapid palliation of patients' symptoms.

	5. Patient is premenopausal or perimenopausal at the time of study entry. a. Premenopausal status is defined as either: • Patient had last menstrual period within the last 12 months. OR • If on tamoxifen within the past 14 days, plasma estradiol and FSH are in the premenopausal range, according to local laboratory definition. • In case of therapy induced amenorrhea, plasma estradiol and/or FSH are in the premenopausal range according to local laboratory definition. • Patients who have undergone bilateral oophorectomy are not eligible. b. Perimenopausal status is defined as neither premenopausal nor postmenopausal 6. Patients must have not received neither prior hormonal therapy nor chemotherapy for advanced breast cancer, except LHRH agonist. Patients who received ≤ 14 days of tamoxifen or a NSAI (letrozole or anastrozole) with or without LHRH agonist for advanced breast cancer prior to randomization are eligible. Patient must have measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (a lesion at a previously irradiated site may only be counted as a target lesion if there is a clear sign of progression since the irradiation).
Key Exclusion criteria	Following are the key exclusion criteria; please refer to Section 5.2 for details and full listing of exclusion criteria. 1. Patient has received prior systemic anti-cancer therapy (including hormonal therapy and chemotherapy, or any CDK4/6 inhibitor for advanced breast cancer. • Patients who received (neo)adjuvant therapy for breast cancer are eligible. If the prior (neo)adjuvant therapy included aromatase inhibitors, the treatment free interval must be greater than 12 months from the completion of aromatase inhibitor treatment until randomization. • If patients have disease recurrence during adjuvant tamoxifen treatment, disease free interval (defined as duration between the dates of patient received complete tumor resection for primary breast cancer lesion to the date of disease recurrence documented) must be greater than 12 months. • Patients who are receiving ≤ 14 days of tamoxifen or NSAI or LHRH agonists ≤ 28 days for advanced breast cancer prior to randomization are eligible. 2. Patient has received extended-field radiotherapy ≤ 2 weeks prior to randomization or limited field radiotherapy ≤ 2 weeks prior to randomization, and has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion). Patient from whom ≥ 25% of the bone marrow has been previously irradiated are also excluded.

	3. Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell skin carcinoma, or curatively resected cervical cancer *in situ*. Note: Central nervous system (CNS) involvement must be ruled out by assessments if a patient has any signs or symptoms indicating potential CNS metastases. 4. Patients who have lung metastases with oxygen demand in resting status. 5. Patients who have liver metastases with bilirubin > 1.5 ULN 6. Patients with CNS involvement unless they meet ALL of the following criteria: • At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment. • Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases. • Leptomeningeal metastases is not allowed, even with stable clinical condition.
Study treatment	For the patients enrolled in the ribociclib group, ribociclib will be given orally once a day on days 1 to 21 of each 28-day cycle. Days 22 to 28 will be a “rest” period from ribociclib. Goserelin will be administered as subcutaneous implant in Day 1 of each 28-day cycle (irrespective of ribociclib treatment cycle). NSAI will be given orally once a day on a continuous daily schedule (e.g., days 1-28 of each 28-day cycle). There will be no “rest” period in the Goserelin or NSAI schedule. Combination chemotherapies of docetaxel + capecitabine, paclitaxel + gemcitabine or capecitabine + vinorelbine will be administer to patients enrolled in the control group. The chemotherapy regimen will be decided by the treating physician.

Investigational/ Control Drug (Name and Strength)	Pharmaceutical dosage form and route of administration	Frequency and/or Regimen
Ribociclib arm (endocrine treatments)		
Ribociclib 600 mg (200 mg × 3)	Tablets for oral use	Days 1-21 of each 28 day cycle
Letrozole 2.5 mg	Tablets for oral use	Daily (all days of every cycle without interruption).
Anastrozole 1 mg	Tablets for oral use	Daily (all days of every cycle without interruption).
Goserelin 3.6 mg	Subcutaneous implant	Day 1 of each 28 day cycle (regardless of ribociclib treatment cycle) with an administration window of ± 3 days
Control arm (combination chemotherapies)		
Docetaxel (60 – 75 mg/m²)/capecitabine (1600 – 2500 mg/m²/day)	Docetaxel: IV Infusion Capecitabine: Tablets for oral use	Docetaxel: once, on day 1 of the 3-weeks cycle, Capecitabine: twice daily, on Days 1 to 14, followed by a 1-week rest period, in 3 weeks cycle.
Paclitaxel (175 mg/m^2)/ gemcitabine (1000 - 1250 mg/m^2) OR Paclitaxel (80 - 90 mg/m^2)/ gemcitabine (800 - 1250 mg/m^2)	IV infusion	Paclitaxel via 3-hour intravenous (IV) infusion on Day 1 in 3-weeks cycles. Gemcitabine at via 30-minute IV infusion on Day 1 and Day 8 in 3-weeks cycles Paclitaxel via 1-hour IV infusion on Day 1 and day 8- in 3-weeks cycles. Gemcitabine at via 30-minute IV infusion on Day 1 and Day 8 in 3-weeks cycles
Capecitabine (1600 - 2500 mg/m^2/day)/vinorelbine (60 to 80 mg/m^2/day [oral] or (25 to 30 mg/m^2 [IV infusion]	Capecitabine: Tablets for oral use Vinorelbine: Capsule for Oral use/IV infusion	Capecitabine: days 1 to Day 14 twice daily, followed by a 1-week rest period, in 3-weeks cycle

	Vinorelbine, once, on Day 1 and Day 8 in 3-weeks cycles Ribociclib, letrozole, anastrozole and goserelin will be administered as a flat-fixed dose, and not by body weight or body surface area. Whereas, combination chemotherapies (docetaxel + capecitabine, paclitaxel + gemcitabine, capecitabine + vinorelbine) will be administered by body surface area; however, less than 10% of change in body surface area will not warrant any change in chemotherapy treatment dose. All study treatment drugs must be administered together at approximately the same time (or within few hours for chemotherapy) each day. Except for ribociclib, all study treatment drugs should be used in accordance with the locally approved label. Ribociclib will be used in accordance to protocol guidelines.
Efficacy assessments	• Computed tomography (CT)/ Magnetic resonance imaging (MRI) (chest, abdomen, pelvis) at screening and then every 6 weeks after randomization for the first 12 weeks and every 8 weeks for the next 32 weeks and at every 12 weeks thereafter until disease progression (radiologically documented according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision. • Brain CT or MRI as clinically indicated. • Whole body bone scan at screening if not performed previously within 42 days (6 weeks) prior to randomization; as clinically indicated thereafter. • Bone x-ray, CT or MRI (if bone lesion at screening) every 6 weeks after randomization for the first 12 weeks and every 8 weeks for the next 32 weeks and at every 12 weeks thereafter until disease progression (radiologically documented according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision. • Skin color photography (if skin lesions at screening) every 6 weeks after randomization for the first 12 weeks and every 8 weeks for the next 32 weeks and at every 12 weeks thereafter until disease progression (according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision. • CT/ MRI for any disease outside of the chest, abdomen, pelvis (if lesion identified at screening) every 6 weeks after randomization for the first 12 weeks and every 8 weeks for the next 32 weeks and at every 12 weeks thereafter until disease progression (radiologically documented according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision. • Survival status every 16 weeks (± 4) weeks or earlier if a survival update is required to meet safety or regulatory needs.
Key safety assessments	• Physical examinations • ECOG performance status • Height, weight, and vital signs • 12 lead ECG

	• Laboratory assessments including hematology, biochemistry, pregnancy (and assessments of fertility) and coagulation
Other assessments	**Patient-reported outcomes:** FACT-B questionnaire will be used to assess health-related quality-of-life, functioning, disease symptoms and treatment-related side effects. [redacted]
Sample size calculation	Based on available data, the median PFS in the control arm is expected to be approximately 12 months. It is expected that treatment with ribociclib arm will result in a 33% reduction in the hazard rate for PFS, i.e., an expected hazard ratio of 0.667 (which corresponds to an increase in median PFS to 18 months under the exponential model assumption). Then in order to ensure 80% power to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: PFS hazard ratio = 0.667, it is calculated that a total of 110 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 10% level of significance, patients randomized to the two treatment arms in a 1:1 ratio. Considering that enrolment will continue for 30 months, 3 patients for 0-6 months, 10 patients for 7-17 months and 6 patients thereafter, a total of 200 patients will be needed to observe the targeted 110 PFS events at about 4 months after the randomization date of the last patient. Assuming 10% drop-out, a total of 222 patients will be needed. The sample size of 222 patients will be randomly assigned to each treatment arm in a 1:1 ratio (111 patients in the experimental arm, 111 patients in the control arm). These calculations were made using the software package East 6.4.
Data analysis	The primary endpoint of the study is PFS. Progression-free survival will be summarized using Kaplan-Meier estimates. Median PFS with 95% confidence intervals will be provided by treatment group. Stratified Cox regression will be used to estimate the hazard ratio (HR) of PFS, along with 95% confidence intervals. In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date. PFS, will be analyzed at the primary analysis (once 110 PFS events are observed) on the FAS. The FAS comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat (ITT) principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure. Full analysis set will be the primary population for all efficacy analyses. As a sensitivity analysis, the distribution of PFS will be compared between the treatment groups using an un-stratified log-rank test and the hazard ratio along with the associated 95% confidence interval resulting from an un-stratified Cox model will be presented.

	The secondary objectives in this study is to compare the two treatment groups with respect to TTF, 3-month treatment failure rate, overall survival (OS), ORR, CBR, and TTR. The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. Overall response rate and its 95% confidence interval will be presented by treatment group. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor, will be used to compare ORR between the two treatment groups. Clinical benefit rate will be summarized for the two treatment groups using descriptive statistics. The Cochran-Mantel Haenszel chi-square test (stratified by randomization stratification factor) will be used to compare the two treatment groups with respect to the CBR. Time to Response and TTF will be listed and summarized by treatment group. Distribution of TTR will be estimated using Kaplan-Meier method if sufficient number of responses are recorded. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety assessments (e.g., electrocardiogram, vital signs) will be summarized by treatment group. The safety analysis set will be used for all safety analysis.
Key words	HR-positive, HER2-negative, advanced breast cancer, ribociclib, NSAI, goserelin, docetaxel + capecitabine, paclitaxel + gemcitabine, capecitabine + vinorelbine, CDK4/6 inhibitors, Phase II, ER-positive, PR-positive, premenopausal, and perimenopausal.

Amendment 2 (04-Mar-2021)

Amendment rationale

The study is currently open for enrollment with 182 patients enrolled to date (10-Feb-2021).

The amendment includes updates for assumptions on the median PFS in the combination chemotherapy arm and ribociclib arm. In the protocol v00, the median PFS was assumed to be 8 months in the combination chemotherapy arm and 12 months in the ribociclib arm. For IA, 61 events was expected to be 15.477 months from the date of first patient randomized in the study. However, only approximately 30 events were observed 18 months from the data of first patient randomization. Based on the assessment and review on the available data, assumptions for median PFS were updated. A summary of key changes proposed in this amendment is listed below:

- Inclusion criterion 4 was amended to clarify that for patients who are eligible under inoperable locally advanced breast cancer or criteria 4c, the recruitment is stopped to enrich patient population with visceral metastases.
- The median PFS assumptions were updated as 12 months in the control arm and 18 months in ribociclib arm, and the significance level was updated from 5% to 10% (one-sided) to maintain the sample size.
- Interim analysis was removed. The rationale to stop early for futility is no longer valid due to increased PFS.
- Patient accrual period was extended to 30 months given slow enrollment due to COVID-19.
- There were tests (laboratory evaluations) mentioned in the original version of protocol, but not applicable to the study, were not part of visit assessment schedule, and now they are being removed for consistency.
- Updated the protocol with program standard language as appropriate.
- Pregnancy follow-up information was added and pregnancy should be followed up to one year after the baby was due to be born.
- Updated the protocol with COVID-19 (Coronavirus) Guidance (Version 3.0, 19-Nov-2020) for ongoing clinical studies.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Abbreviations: added ABC, ESMO-MCBS, GCSF, HR+ and LHRH.
- Glossary of terms: removed mis-randomized subjects.
- [redacted]
- Protocol summary: made few edits in study design, key exclusion criteria and efficacy assessments.
- Protocol summary: amended key inclusion criterion 4 and 4c.
- Protocol summary: updated study treatment including an administration window for goserelin and dose frequency for capecitabine, gemcitabine and vinorelbine.

- Protocol summary: key safety assessments (added assessments of fertility and coagulation and deleted hepatic safety markers) to match with Section 8.4.2 (laboratory evaluations).
- Protocol summary: updated median PFS assumptions and removed the text that mentions interim analysis.
- Protocol summary: data analysis (updated PFS events to 110 for primary analysis, removed the text that mentions one sided level of significance and updated with randomization stratification factor for consistency with Section 12.5.1).
- Section 1.1.2, Section 1.1.4.1.4 and Section 1.2: updated the overall survival data with recent data.
- Section 1.1.2: amended ribociclib indication and usage as per FDA prescribing information, added ABC 5 guidelines with the recommendation for ribociclib use for premenopausal patients with ESMO-MCBS score 5 and EMA recommendations for ribociclib use.
- Section 1.1.4.1.4: updated subgroup analysis of Asian patients (MONALEESA-7).
- Section 3: updated survival follow up duration, and total enrollment period.
- Section 3.1.2 and Section 3.1.3: updated end of study duration.
- Section 3.1.3: clarified that survival follow-up will be conducted after the end of safety follow-up and updated the overall survival events.
- Section 3.1.4, Section 3.17, Section 4.4, Section 4.5.1, Section 12 and Section 12.7: removed the text that mentions planned futility interim analysis.
- Section 3.1.7: updated definition of end of study and wording related to post trial access.
- Section 4.3: updated Table 4-1 to add administration window for goserelin and dose frequency for vinorelbine.
- Section 4.5.1: added guidance wording during public health emergencies.
- Section 5.1: amended inclusion criterion 4 and 4c.
- Section 5.2: exclusion criteria 2 was modified to clarify the duration of extended-field radiotherapy prior to randomization.
- Section 6.1.1: updated Table 6-1 to add administration window for goserelin and dose frequency for capecitabine.
- Section 6.1.4.1: added administration window for goserelin.
- Section 6.1.4.2: added missing the information for gemcitabine dose, added additional wording regarding switch between Vinorelbine oral capsule and Vinorelbine IV infusion and corrected vinorelbine pharmaceutical dosage form and route of administration.
- Section 6.1.7: corrected treatment duration.
- Section 6.2.1: removal of censored reason for patients who received either megestrol acetate or medroxyprogesterone for more than one month of treatment.
- Section 6.3.2: corrected wording regarding treatment assignment using IRT.
- Section 6.5.1.3: added administration window for goserelin.
- Section 6.7 and Section 7: added guidance wording during public health emergencies.
- Section 8: corrected wording for patients who prematurely discontinue the study, updated visit window for EOT visit and safety follow up visit and administration window for

goserelin. Table 8-1 is updated to clarify survival follow up timeline, added administration window for goserelin and added guidance wording during public health emergencies.

- Section 8.1: corrected typos for laboratory evaluations and ECG.
- Section 8.3.1: clarified wording for treatment discontinuation and updated survival duration.
- Section 8.3.2: added additional wording for imaging assessments for consistency with Table 8-2, corrected tumor evaluation criteria at EOT and updated Table 8-2 with additional wording for treatment phase for bone X-ray, CT or MRI and skin color photography.
- Section 8.4: deleted hepatic safety markers and added pregnancy and coagulation to match with Table 8-5. Also, added guidance wording during public health emergencies in Table 8-3.
- Section 8.4.2: added guidance wording during public health emergencies in Table 8-5.
- Section 8.4.2.3: added wording for clarity in case of positive pregnancy test.
- Section 8.4.2.3, Section 8.4.3, Section 8.5 (Table 8-7) and Section 10.1.1: added guidance wording during public health emergencies.

[redacted]

- Section 9.1.1: addition of discontinuation reasons according to Section 16.4.2 for consistency i.e., non-compliant with study treatment and no longer requires treatment.
- Section 9.2: corrected end of study duration and number of PFS events for primary analysis. Also, updated wording related to safety evaluation following last dose or EOT visit and post-trial access.
- Section 10.1.4: added follow-up information that pregnancy should be followed up to one year after the baby was due to be born.
- Section 11.2: updated wording for management of database and quality control.
- Section 12.4.2: number of PFS events for primary efficacy variable analysis was updated.
- Section 12.4.3: added heading style (Handling of missing values/censoring/discontinuations) and description related to start of new anti-cancer treatment.
- Section 12.4.4: added description related to additional sensitivity analysis.
- Section 12.5.3:
  - removed ‘no formal statistical test will be performed for patient reported outcomes (PRO) data’.
  - added ‘time to deterioration in the PRO scales will be performed and compared between the two treatment arms’.

[redacted]

- Section 12.8: sample size calculation section was updated based on the updated assumptions for median PFS.

- Section 15: updated list with 3 additional references and in alphabetical order.
- Section 16.1: added text related to Table 16-1 and 16-2, respectively, for list of prohibited medications and medication to be used with caution during combined ribociclib, NSAI, and goserelin treatment in this study.
- Section 16.1: updated Table 16-2 with the list of medications to be used with caution during study treatment as per program standard language.
    - addition of 'dabrafenib' and removal of 'efavirenz' under the category of moderate CYP3A4/5 inducers.
    - addition of 'aprepitant' and 'perospirone' under the category of sensitive CYP3A4/5 substrates.
    - addition of 'atorvastatin' and removal of 'atazanavir' under the category of BSEP inhibitors.
    - addition of 'irinotecan' under the category of BCRP substrates.
- Section 16.4.2: addition of discontinuation reasons according to Section 9.1.1 for consistency.
- Section 16.5: reference list arranged according to alphabetical order.
- Section 16.6: added heading style for Appendix 3.
- Typographical and grammatical errors, and inconsistencies between different sections were addressed throughout the protocol.
- The term "subject" was changed to "patient" throughout the protocol.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent and Pregnancy Follow up Consent. Sites are required to update and submit for approval a revised Informed Consents that takes into account the changes described in this protocol amendment.

Amendment 1 (27-Jan-2020)

The study is currently open for enrollment with 66 patients enrolled to date.

The current amendment is primarily intended for [redacted] clarify specific aspects of original protocol version, based on feedback and communications received from investigators and the participating countries.

A summary of the key changes proposed in this amendment is listed below:

[redacted]

- An additional exclusion criterion was added to exclude patients, who have disease recurrence during adjuvant tamoxifen treatment within 12 months period.
- A new secondary objective "to compare 3-month treatment failure rate" was added to help in understanding the early efficacy of the regimen, as advised by the steering committee.
- The clinical safety and efficacy data was updated for ribociclib in line with newly reported results of CLEE011E2301 (MONALEESA-7) and CLEE011F2301 (MONALEESA-3) studies.
- Additional clarification was included on adjustment of ribociclib treatment cycles in the case of dose interruptions/re-initiation.
- Additional wording for imaging tumor assessments was added for those patients who discontinued treatment.
- Additional wording was added for combination chemotherapy arm patients to clarify that they might have additional biochemical assessments as per the local practice for such drugs and those are to be considered as standard of care.
- Follow-up guidance for interstitial lung disease/pneumonitis was added.
- Guidance for other adverse reactions was updated to include Toxic Epidermal Necrolysis (TEN).
- Planned method of analysis for patient reported outcomes (FACT-B) was changed.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Throughout protocol: Typographical, inconsistencies between different sections and grammatical errors were addressed.
- Throughout protocol: Added the wording "radiologically documented according to RECIST 1.1 criteria" throughout to clearly define disease progression.
- Abbreviations: Added BSA, FFPE, modified RAP/SAP
- Protocol summary: Added phase of the clinical trial

- Protocol summary: Added goserelin dose administration details.
- Protocol summary was updated to maintain consistency with the main body of the protocol.
- Section 1.1.1: the prevalence and mortality rates of breast cancer in Asia were updated to reflect the GLOBOCAN 2018 data.
- Section 1.1.2 was updated to add latest overall survival data from CLEE011E2301 (MONALEESA-7) study.
- Section 1.1.4.1 was updated to reflect the latest health authority approval status of ribociclib.
- Section 1.1.4.1.4 was updated to added latest clinical efficacy data from CLEE011E2301 (MONALEESA-7) and CLEE011F2301 (MONALEESA-3) studies.
- Section 1.1.4.6 was updated to add additional citations.
- Section 1.2 was updated to accommodate the latest efficacy data emerged from the ongoing trials for ribociclib and palbociclib.
- In Table 2-1, definition of secondary endpoint of time to treatment failure was updated to include “change to other anti-cancer therapy”.
- Table 2-1 was updated to accommodate the additional secondary [redacted] objectives and endpoints.
- Figure 3-1 was updated to mention that treatment phase of chemotherapy arm will be of 21 days and the footnote was updated to make the radiological assessment schedule consistent with the other sections of protocol.
- Section 3 was updated
  - to bring more clarity how long the patients can remain in the study if they permanently discontinue ribociclib
  - [redacted]
  - to update the number of sites and participating countries
  - composition of steering committee was updated to maintain the consistency with the other sections of protocol
- Section 3.1.2.1 was modified to remove the text that mentions the efficacy follow up for patients who discontinued the protocol study treatment without disease progression and not censored yet.
- Section 3.1.7 was updated to reflect the correct eCRF page that need to be completed at the end of study and the name of Managed Access Program” was also changed to “post-trial access”.
- Table 4-1 was updated to provide more clarity that ribociclib 600 mg dose will be administered via 3 tables of 200 mg each.
- Section 4.5.1 and Section 10.2.2 was updated to reflect the composition of steering committee to maintain the consistency with other sections of the protocol.
- Section 5.1 was updated
  - The term “subject” was changed to “patient”

  - Inclusion criterion 4 was modified to bring more clarity and maintain consistency with protocol title.
  - Inclusion criterion 5 was modified to remove the pre-specified concentration ranges for plasma estradiol and FSH
  - Inclusion criterion 8 was modified to add additional condition for total bilirubin in patients with liver metastases.
  - Inclusion criterion 8 was modified to remove sodium and phosphorus from the list of laboratory parameters that have to be in the normal range, before the first dose of study medication
- Section 5.2 was updated
  - Exclusion criterion 1 was modified to exclude patients, who have disease recurrence during adjuvant tamoxifen-treatment within 12 months period.
  - Exclusion criteria 4 was modified to exclude patients who participate in any other type of medical research that judged not to be scientifically or medically compatible with this study.
  - Exclusion criterion 10 was modified to update the unit for bilirubin in patients who have liver metastases.
  - A new exclusion criterion (criterion no. 14) “Patient is concurrently using hormone replacement therapy” was added.
- Exclusion criterion 7 was modified to remove barrier methods of contraception.
- Section 6.1 was modified to clarify that investigational drugs labels will be approved by the local regulatory authorities, if required by country regulation.
- Table 6-1 and Section 6.1.4.1 was updated to clarify that goserelin dosing frequency will remain unchanged, regardless of ribociclib treatment cycle.
- In Section 6.1.1 was modified to clarify that ribociclib will be used in accordance to protocol guidelines and all study treatment drugs (except ribociclib) should be used in accordance with the locally approved label.
- Section 6.1.3 was updated to include beta-blocker in the list of exempted drugs that are allowed in this trial.
- Section 6.1.6 was updated to clarify that leuprorelin or other LHRH agonists dosing will be as per the local approved label.
- Section 6.2.15 was modified to mention that cumulative courses of RT should not encompass ≥ more than 25% of the irradiated bone marrow, instead of > 25% of the irradiated bone marrow.
- Section 6.2.1.7 was added to clarify that the beta-blocker could be used to correct tachycardia considering the inclusion criteria and the prevalence of tachycardia in breast cancer population.
- Section 6.3.2 and Section 11.2 were updated to remove the text related to IRT assisted randomization.
- Section 6.5.1.1.1 was inserted to provide more clarity on adjustment of ribociclib treatment cycles in case of dose interruptions/re-initiation.

- Section 6.5.1.1.4 was inserted to provide follow-up guidance for interstitial lung disease/pneumonitis.
- Section 6.5.1.1.5 was updated to clarify that ribociclib dose adjustment and management recommendations (provided in Table 6-6) are applicable for all other adverse events, including toxic epidermal necrolysis.
- Section 6.5.3.2, Section 6.5.3.3, Section 6.5.3.5 was updated to clarify that for chemotherapy treatment to begin, blood tests may be performed that are part of local practice and standard of care.
- Section 6.5.3.5 was updated to provide more clarity about the impact (on study) of vinorelbine treatment discontinuation due to hematologic toxicities and non-hematologic toxicities.
- Table 6-11 was removed as Table 6-8 already provides the similar information for dose reductions of docetaxel. Thereafter, all table numberings are revised in the protocol.
- Section 6.6.1 and Section 6.7.1.1 was updated to mention that treatment compliance will also be captured in the "site source document", in addition to the "Drug Accountability Form".
- [redacted]
- Section 8 was updated to remove the text that indicates missed or rescheduled visits would not lead to automatic discontinuation. Inserted a text clarifying that a visit window of ± 7 days is allowed for biochemistry assessments. Additional modifications were also done for more clarity and to maintain the consistency with other section of the protocol.
- Table 8-1 was updated to mark that
  - [redacted]
  - Information on estradiol and FSH will be remain in source documents only (S) and will not be entered into the database (D).
- Footnote of Table 8-1 was updated
  - To mention that for patients on combination chemotherapy may have additional hematology and biochemical assessments as per the local practice for such drug and are considered as standard of care
  - To clarify that coagulation parameters of INR or PT are to be performed at every visit only for the patients receiving oral coumarin-derivate anticoagulants such as warfarin and phenprocoumon along with capecitabine as one of the medication in the combination chemotherapy group.
- Section 8.1 was updated to clarify that
  - ECG should be performed within 7 days prior to randomization.
  - The modification also includes multiple evaluations of liver function and renal function is also allowed in addition to electrolytes and blood counts for screen failure patients.
- Section 8.1.2 was updated to include visit date to maintain consistency with eCRF
- Section 8.2 was updated to maintain consistency with eCRF.
- Section 8.3.1 was updated to maintain consistency with the other sections of protocol.

- Section 8.3.2 was updated to clarify about the imaging tumor assessments for patients who discontinued treatment.
- Section 8.3.2 was updated to remove text that indicated that repeat assessment will be performed to confirm CR and PR after the criteria for objective response are first met.
- Section 8.4.2 was updated as there is no laboratory manual being used in this study. Also a text was inserted clarifying that a visit window of ± 7 days is allowed for biochemistry assessments.
- Table 8-5 was updated to maintain consistency with eCRF in terms of laboratory parameters that are being assessed in the study. This table was also modified to remove sodium and phosphorus from the list of laboratory parameters
- Section 8.4.2.1 and Section 8.4.2.2 were updated to clarify that patients enrolled in the chemotherapy treatments might have additional blood tests that are part of local practice and standard of care.
- In Section 8.4.2.3 was updated to mention that there would be no need to repeat the pregnancy test if screening assessments were performed ≤ 7 days prior to the first dose of study treatments.
- Section 8.4.2.4 was updated to capture the requirement of coagulation testing for patients receiving capecitabine.
- Section 8.4.3 was updated to clarify that single reading of ECG is required.
- Section 8.5 was updated to modify the window period for FACT-B questionnaire from 3 days to 7 days.
- [redacted]
- Section 9.1.1 was updated to reflect the latest protocol standard language document.
- Section 9.2 was updated to remove duplication.
- Section 11.1 was updated to remove duplication.
- Section 12.5.1 was updated to describe the statistical analysis plan for the newly added secondary efficacy objective of 3-month treatment failure rate.
- Section 12.5.3 was updated as the planned method of analysis for FACT-B was changed to be aligned with endpoint defined in Section 2.
- [redacted]
- Section 16.4.2 was updated to revise the scheduled date of the end of treatment visit to be consistent with other sections of protocol.
- Table 16-1 and Table 16-2 in Appendix 1 were updated to reflect the latest list of prohibited medication and medications to be used with caution during study drug treatment.
- Appendix 3 was updated to replace FACT-B + 4 questionnaire with FACT-B questionnaire

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

1 Introduction

1.1 Background

1.1.1 Epidemiology

Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers), corresponding to a rate of 43 per 100,000 patients. Of these, approximately a quarter (24%) of all breast cancers were diagnosed within the Asia-Pacific region (approximately 404,000 cases at a rate of 30 per 100,000). Breast cancer ranks as the fifth cause of death from cancer overall. About 522,000 females (13 per 100,000 population) were estimated to have died from breast cancer globally during 2012, including almost 116,000 deaths (22%) throughout the Asia-Pacific region at a rate of 8 per 100,000. It is the most common cancer in women both in more and less developed regions with slightly more cases in less developed (883,000 cases) than in more developed (794,000) regions. Worldwide, cancer rates are increasing and per the GLOBOCAN 2018 report on cancer incidence and mortality statistics, the 5-year prevalence is estimated to be 2,623,745 in Asia, with a mortality of 310,577. The percentage of patients with breast cancer aged younger than 50 years could be as high as 42% in the Asia-Pacific region, and is almost 50% in the Middle East compared to 33% in the global scenario (El-Saghir et al 2007; GLOBOCAN 2018; Youlden et al 2014).

Invasive breast cancer is classified by the presence or absence of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) antigen for prognostic and treatment purposes. Approximately two-thirds of breast cancers in women aged 50 years or younger are hormone receptor (HR)-positive (defined by expression of the estrogen and/or progesterone receptor) and human epidermal growth factor receptor 2 (HER2)-negative (Howlader et al 2014). For first-line treatment of HR-positive, HER2-negative advanced breast cancer (ABC), although the recommendation is to provide endocrine therapy first in general (Rugo et al 2016), a high proportion of patients (younger than 50 years) are still being prescribed chemotherapy, which was associated with worse outcome, even after adjustment of relevant prognostic factors (Lobbezoo et al 2016). Therefore, dedicated trials in premenopausal breast cancer are required to establish the efficacy of endocrine treatment based therapy compared with chemotherapy in this population.

1.1.2 Treatment options for premenopausal women with hormone receptor positive (HR+), HER2-negative premenopausal advanced breast cancer

Endocrine therapy remains the therapeutic backbone for the treatment of HR+, HER2-negative breast cancer. Based on current treatment guidelines (Gradishar et al 2017), for premenopausal women with HR+, HER2- negative, advanced breast cancer, the standard treatment options are selective ER modulators (tamoxifen or toremifene) or ovarian ablation or suppression plus endocrine therapy.

The efficacy and safety of the combination of ribociclib and either tamoxifen or a nonsteroidal aromatase inhibitor (letrozole or anastrozole) and goserelin (Zoladex) as first line treatment was evaluated in MONALEESA-7 study, a phase III, multicenter study in pre- and perimenopausal women with HR+, HER2-negative advanced (metastatic or loco regionally recurrent) breast

cancer who have not received prior therapy for their disease. The study met its primary objective at the pre-planned interim analysis; progression-free survival (PFS) was significantly improved in the ribociclib arm (median: 23.8 months) compared with the placebo arm (median: 13.0 months). Clinical benefit was evident relative to placebo plus letrozole with a 44.7% estimated risk reduction in the primary PFS endpoint as per investigator assessment evaluated by RECIST version 1.1 (HR=0.553, 95% confidence interval (CI): 0.441-0.694; $p = 9.83 \times 10^{-8}$) (Tripathy et al 2018). Overall survival (OS) was significantly longer in the ribociclib arm than in the placebo arm, with a 29% relative reduction in the risk of death (HR=0.712; 95% CI: 0.535, 0.948). The one-sided stratified log-rank test P value was 0.00973, which crossed the pre-specified stopping boundary (p=0.01018) to claim superior efficacy (Im et al 2019). The recent updated median overall survival was 58.7 months with ribociclib + endocrine therapy and 48.0 months with placebo + endocrine therapy (HR, 0.76; 95% CI, 0.61-0.96), with a 24% relative reduction in the risk of death with ribociclib. It is the longest reported period in HR+/HER2-negative advanced breast cancer (ABC) among all Phase III trials in this setting (Tripathy et al 2020).

Expanded indication based on MONALEESA-3 (CLEE011F2301) and MONALEESA-7 (CLEE011E2301) approved by USFDA on 18-Jul-2018. The supplemental New Drug Application approval for Ribociclib (KISQALI®) is the first industry-wide approval using the USFDA's Real Time Oncology Review and the Assessment Aid pilot programs and was approved within one month of submission.

The USFDA also granted breakthrough therapy designation for MONALEESA-7 and priority review for the MONALEESA-3 and 7 for expanded indication. Ribociclib has been approved in combination with aromatase inhibitor in pre/perimenopausal or postmenopausal women and with fulvestrant pre- and/or postmenopausal women. Additional detail expanded indication are provided in Section 1.1.4.6. Furthermore, according to new updated ABC 5 guidelines using the current available data and follow-up, the ESMO-MCBS score was 5 (efficacy score 4 [PFS and OS]: 4; improved QoL) for the use of ribociclib combined with endocrine therapy in the first-line setting in pre-menopausal patients (Cardoso et al 2020).

The USFDA has granted approval for ribociclib combination:

- with an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with HR+, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or
- fulvestrant for the treatment of postmenopausal women with HR+, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

EMA has granted approval for ribociclib:

- for the treatment of women with HR+, HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy and
- in pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist.

1.1.3 Role of the CDK4/6 pathway in breast cancer

While endocrine therapy is effective in treatment of HR+ advanced breast cancer, approximately 30-50% of patients may not respond to it due to a primary resistance. Moreover, many advanced breast cancer patients with initial response to endocrine therapy will acquire secondary resistance to these agents (Bachelot et al 2012; Nichols et al 2015). Co-targeting the ER with other key intracellular proliferation and cell survival signaling pathways, such as mechanisms responsible for cell cycle regulation and progression may enhance first-line endocrine responsiveness of endocrine therapy tumors by preventing or delaying the development of acquired resistance for endocrine treatments.

Cell cycle progression is directly regulated by cyclin-dependent serine-threonine protein kinases (CDKs). Extracellular growth and adhesion signals increase the level and function of cyclin D proteins within the cell. In turn, the cyclin D proteins associate with and activate CDK4 and CDK6 (Musgrove et al 2011). CDK4 and CDK6 phosphorylation leads to inactivation of the retinoblastoma protein (pRb) and thus releases E2F which in turn leads to the transcription initiation of proteins involved in cell cycle propagation and cell proliferation. The luminal A and B subtypes of breast cancer (85% of which are ER+/HER2-negative) have high rates of cyclin D/CDK activation; in the luminal A and B subtypes, cyclin D1 (CCND1) amplifications were observed in 29% and 58%, and CDK4 amplifications were observed in 14% and 25% respectively (Holm et al 2012; The Cancer Genome Atlas Network 2012). The luminal A subtype tumors also have loss of CDKN2A, which encodes p16Ink4a, a CDK inhibitor (Beroukhim et al 2010). The luminal subtypes also maintain expression of Rb, which is essential for benefit from treatment with a CDK4/6 inhibitor (Thangavel et al 2011).

Dysregulation of cell cycle checkpoints is common in cancer. Modulating the cell cycle has always been an attractive therapeutic target in cancer, and previously published data have suggested that CDK4/6 inhibition may play a key role in the treatment of subsets of breast cancers. Patients with HR+ breast cancer exhibiting a gene expression signature of Rb loss had shorter recurrence-free survival following adjuvant tamoxifen (Bosco et al 2007). A tumor gene expression signature of E2F activation was associated with higher residual tumor cell proliferation following pre-surgical AI therapy. Therefore, activation of the CDK4/CDK6/E2F axis promotes endocrine resistance, and treatment with a CDK4/6 inhibitor or knockdown of CDK4 expression abrogates endocrine-resistant cell proliferation.

In conclusion, loss of cell cycle control is a hallmark of cancer, and aberrations in the cyclin/CDK/Rb pathway are common in metastatic luminal breast cancer. Consequently, inhibition of this pathway at the level of CDK4/6 leads to reactivation of Rb and binding of E2F, thus leading to cell cycle arrest. Therefore, co-targeting the CDK4/6-Rb-E2F pathway with CDK4/6 inhibitors may be a viable strategy to enhance endocrine responsiveness and prevent or delay the development of acquired as well as the do-novo endocrinal resistance.

The marked efficacy of CDK4/6 inhibitors in combination with endocrine therapy in the treatment of both pre and post-menopausal patients with HR+, HER2-negative advanced breast cancer has been consistently documented in several recent phase III randomized trials. Importantly the PFS data as well as the overall response rate (ORR) data were quite favorable, when compared to what may be achieved by chemotherapy treatment in these patients.

1.1.4 Introduction to investigational treatment(s) and other study treatment(s)

This study includes ribociclib, goserelin, NSAI (letrozole or anastrozole), and chemotherapies (docetaxel, capecitabine, paclitaxel, gemcitabine, and vinorelbine) as treatments.

1.1.4.1 Ribociclib

Ribociclib is an orally bioavailable and highly selective small molecule inhibitor with highly specific nanomolar inhibitory activity against CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with IC50's of 0.01 and 0.039 µM in biochemical assays, respectively.

Ribociclib (Kisqali®) in combination with an aromatase inhibitor (or letrozole, as specified by individual Health Authority marketing authorization) as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer was approved by the USFDA on 13-Mar-2017, and by the European Commission on 22-Aug-2017 and a number of additional marketing authorizations in this indication have been approved globally.

On 18-Jul-2018, the U.S. FDA expanded the indication for ribociclib in combination with an AI to include pre/perimenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy and ribociclib in combination with fulvestrant for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on ET (MONALEESA-7 [CLEE011E2301] and MONALEESA-3 [CLEE011F2301], respectively). This expanded indication was subsequently approved by the EU Commission on 17-Dec-2018 and in several additional countries globally. Health authority reviews are currently ongoing, with additional marketing approvals expected in HR-positive, HER-2 negative advanced or metastatic breast cancer on an ongoing basis worldwide. Additional information on ribociclib approval is available in Section 1.1.2.

1.1.4.1.1 Non-clinical experience

Ribociclib inhibits the phosphorylation of Rb at CDK4/6-binding sites with an average IC50 of 60 nM in Jeko-1 mantle cell lymphoma cells that overexpress cyclin-D1. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of ribociclib requires the presence of functional retinoblastoma protein.

Cardiac safety studies in vivo demonstrated QT prolongation with the potential to induce premature ventricular contractions at higher exposure levels. The effects of ribociclib on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), the kidney (concurrent degeneration and regeneration of tubular epithelial cells), skin (atrophy), bone (decreased bone formation) and testes (atrophy) are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition. The hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) was identified as an additional target organs of toxicity that are not likely related to the primary pharmacology of ribociclib. Generally, all these effects of ribociclib demonstrated either reversibility or a clear trend towards reversibility. Ribociclib did not show an indication for a genotoxic potential. Reproductive studies in animals have demonstrated that ribociclib is embryotoxic, fetotoxic, and teratogenic.

In vitro, ribociclib was a reversible inhibitor of human cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. Under therapeutic conditions, inhibition of CYP3A4 is likely to occur, while inhibition of CYP1A2 or CYP2E1 is not expected. The in vitro inhibitory potency of ribociclib for the transporters breast cancer resistance protein (BCRP), organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein-1 (MATE1), and bile salt export pump (BSEP) may translate into clinically relevant inhibition at therapeutic doses.

Elimination of ribociclib is dominated by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). Although ribociclib is a substrate of the P-glycoprotein efflux transporter, this process is likely not clinically relevant due to the high passive permeability of ribociclib.

1.1.4.1.2 Clinical experience

Ribociclib is currently being investigated in patients with breast cancer and other solid tumors in multiple clinical trials at different phases of development.

1.1.4.1.3 Clinical safety of ribociclib

Clinical safety of ribociclib with endocrine agents such as letrozole, anastrozole, tamoxifen, exemestane and fulvestrant has been being evaluated in several phase I and III combination trials. Except in Japanese patients, the recommended dose of ribociclib in combination with these agents was declared as 600 mg every day on a 3 weeks on/1 week off schedule; in Japanese patients, 300 mg every day on the same dosing schedule was declared.

Safety profile of ribociclib in combination with letrozole was investigated in a randomized clinical trial of ribociclib and letrozole versus placebo and letrozole [CLEE011A2301] in 668 treatment-naive postmenopausal women with HR+, HER2-negative, advanced breast cancer. Most common treatment-emergent adverse events reported in the ribociclib arm in this study occurring in >30% of patients were neutropenia (74.3%), nausea (51.5%), infections (50.3%), fatigue (36.5%), diarrhea (35.0%), alopecia (33.2%) and leukopenia (32.9%). The most common grade 3 or 4 adverse events reported in ≥ 5% of patients in the ribociclib arm were neutropenia (59.3%), leukopenia (21.6%), hypertension (9.9%), increased alanine aminotransferase (ALT) (9.3%), lymphopenia (6.9%) and increased aspartate aminotransferase (AST) (5.7%). Febrile neutropenia occurred in 1.5% of the patients in the ribociclib arm. Four patients (1.2%) met the biochemical and clinical criteria for Hy's Law with 3 reported as treatment-related and all 4 returned to normal values after treatment discontinuation. Eleven patients (3.3%) presented on treatment QTc using Fridericia's formula (QTcF) prolongation > 480 msec. Serious adverse event were reported in 21.3% of patients in the ribociclib arm with 7.5% of serious adverse events deemed by investigators as treatment-related. There were 3 fatal events in the ribociclib arm (disease progression, sudden death, and unknown cause) with 1 adverse event (sudden death) reported as treatment-related in a patient who had grade 3 hypokalemia and grade 2 QTcF prolongation (483 msec). Neutropenia, QT interval prolongation and hepatobiliary toxicity are considered to be important identified risks for ribociclib which appear to be manageable and reversible with adequate monitoring, interruption and/or reduction of ribociclib dosing.

In MONALEESA-7, AEs of any grade with ribociclib regardless of causality (reported in ≥ 20% of patients) were neutropenia (75.8%), hot flashes (34%), nausea (31.6%), and leukopenia (31.3%). Febrile neutropenia occurred in 2.1% of patients. Increased ALT and AST (any grade) were reported in 12.8% and 11.9% of patients, respectively, with no cases of Hy's Law (Tripathy et al 2018).

In MONALEESA-7, a higher incidence of notable QTcF values and change from baseline QTcF (ΔQTcF) were observed in patients receiving tamoxifen compared to NSAI as the combination partner in both the placebo and ribociclib groups. Based on QTcF data with tamoxifen in MONALEESA-7, ribociclib will not be used combination with tamoxifen in this study. In patients receiving the combination of ribociclib, NSAI and goserelin, the mean ΔQTcF on Cycle 1 Day 15, 2 hours post dose was 18.6 msec. The mean ΔQTcF values in MONALEESA-7 are consistent with MONALEESA-2 where ΔQTcF prolongation from baseline of 19.6 msec (90% CI: 18.0-21.2) was observed at Cycle 1 Day 15, 2 hours postdose in the ribociclib arm.

In MONALEESA-3, the most common all-grade adverse events (AEs) reported in ≥ 30% of patients were neutropenia, nausea, and fatigue. The most common grade 3 AEs occurring in ≥ 10% of patients were neutropenia and leukopenia. The only grade 4 event reported in ≥ 5% of patients was neutropenia. Febrile neutropenia occurred in 1.0% of patients in the ribociclib plus fulvestrant arm versus 0% of patients in the placebo plus fulvestrant arm. Most AEs observed were of mild or moderate severity, with no new safety signals observed. Although neutropenia was the most common all-grade and grade 3 or 4 AE, these events were generally uncomplicated. AE-related treatment discontinuations were rare, further supporting the manageable safety profile of ribociclib-based combinations. The incidence of QTcF prolongation observed with ribociclib plus fulvestrant was similar to that previously reported with ribociclib and there were no incidences of torsades de pointes (Slamon et al 2018).

For a comprehensive review of safety profile of ribociclib in combination with endocrine agents refer to the ribociclib Investigator's Brochure (IB).

1.1.4.1.4 Clinical efficacy with ribociclib

In a phase III randomized clinical trial of ribociclib and letrozole versus placebo and letrozole (CLEE011A2301) in 668 treatment-naive postmenopausal women with HR+, HER2-negative, advanced breast cancer, ribociclib improved PFS (HR 0.56, 95% CI: 0.43-0.72, p = 0.00000329). The investigator-reported ORR was 40.7% (95% CI: 35.4%-46.0%) in the ribociclib arm and 27.5% (95% CI: 22.8%-32.3%) in the placebo arm (p = 0.000155) in the full analysis set (FAS); and 52.7% (95% CI: 46.6%-58.9%) and 37.1% (95% CI: 31.1%-43.2%) (p = 0.00028) in patients with measurable disease at baseline (Hortobagyi et al 2016).

For the postmenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer, ribociclib plus fulvestrant might represent a new first or second-line treatment option. Results from the recently completed MONALEESA-3 trial proved that ribociclib plus fulvestrant significantly improved the median progression-free survival compared with the placebo plus fulvestrant: 20.5 months (95% CI: 18.5-23.5 months) versus 12.8 months (95% CI: 10.9-16.3 months), respectively (hazard ratio = 0.593; 95% CI: 0.480-0.732; p<0.001) (Slamon et al 2018). A statistically significant improvement in overall survival benefit with addition of ribociclib was observed, with 28% reduction in the relative risk of death (HR: 0.724; 95% CI: 0.568 – 0.924, p = 0.00455) (Slamon et al 2019).

Similarly, Ribociclib plus endocrine therapy could represent a new first-line treatment option in premenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer. Results from the MONALEESA-7 trial demonstrated that median progression-free survival was significantly improved in the ribociclib plus endocrine therapy group (23·8 months; 95% CI: 19·2–not reached) compared with the placebo plus endocrine therapy group13·0 months (11.0 to 16·4) (hazard ratio = 0·55, 95% CI: 0·44-0·69; p<0·0001) (Tripathy et al 2018). Results emerged out of the protocol-specified second interim analysis for overall survival demonstrate that the addition of ribociclib to endocrine therapy resulted in significantly longer overall survival than endocrine therapy alone. The estimated overall survival at 42 months was 70.2% (95% CI: 63.5 to 76.0) in the ribociclib group and 46.0% (95% CI, 32.0 to 58.9) in the placebo group (hazard ratio for death = 0.71; 95% CI, 0.54 to 0.95; p = 0.00973 by log-rank test). The significantly longer progression-free survival in the ribociclib group than in the placebo group and the approximately 29% lower risk of death in the ribociclib group in this report show that there is a substantial clinical benefit of ribociclib plus endocrine therapy as compared with endocrine therapy alone (Im et al 2019). After a median of 53.5 months follow-up, median overall survival for patients taking ribociclib + endocrine therapy was 58.7 months and 48.0 months for endocrine therapy alone (HR, 0.76; 95% CI, 0.61-0.96), with a 24% relative reduction in the risk of death with ribociclib. It is the longest reported period in HR+/HER2-negative ABC among all Phase III trials in this setting (Tripathy et al 2020).

Refer to the ribociclib Investigator's Brochure for additional details on efficacy profile.

1.1.4.1.5 Clinical pharmacokinetics of ribociclib

Following oral dosing of the capsule formulation at 600 mg, ribociclib is rapidly absorbed with median time of maximum concentration (Tmax) of 2.40 h (range: 0.683 to 7.82 h). Steady-state plasma peak blood concentration (Cmax) ranges from 606-6170 ng/mL (geometric mean: 1820 ng/mL or 4.1 μM) and AUC0-24h ranges from 6770-90600 ng*h/mL (geometric mean: 23800 ng*h/mL). The elimination half-life (T1/2) of ribociclib is 32.0 h (range: 8.06 to 97.9 h). Inter-patient variability in Cmax and area under the curve (AUC) is 62% and 66%, respectively, as assessed by geometric coefficient of variation (CV). LEQ803, an active metabolite of ribociclib, has similar pharmacokinetics (PK) characteristics as parent drug. At the 600 mg dose level, LEQ803 accounts for approximately 8% of parent exposure after single and multiple doses. Neither ribociclib nor LEQ803 accumulate substantially following repeated daily administration.

Ribociclib undergoes extensive hepatic metabolism via CYP3A in humans based on in vitro and in vivo studies. Ribociclib is mainly eliminated via hepatic clearance, with renal clearance playing a lesser role in humans. The majority of the administered dose was excreted in feces (69.1%), with a minor amount excreted in urine (22.6%). Ribociclib accounted for approximately 23% of the total radioactivity in plasma. The most prominent metabolites in plasma are CCI284 (N-hydroxylation), LEQ803 (N-demethylation), and M1 (secondary glucuronide), each representing <10% of total radioactivity. The clinical activity (pharmacological and safety) of ribociclib is primarily due to parent drug, with a negligible contribution from circulating metabolites.

Concomitant use of ribociclib with strong CYP3A4 inhibitors or strong CYP3A4 inducers should be avoided as ribociclib exposure may be markedly affected. Co-administration of a

strong CYP3A4 inhibitor [redacted] increased ribociclib AUC by 3.2-fold following a single oral dose of 400 mg ribociclib (CLEE011A2101). Co-administration of a strong CYP3A4 inducer [redacted] decreased ribociclib AUCinf by 89% following a single oral dose of 600 mg ribociclib (CLEE011A2101).

Ribociclib is a moderate to strong inhibitor of CYP3A4, but did not have a substantial effect on CYP1A2 substrates in humans [CLEE011A2106]. Co-administration of [redacted](CYP3A4 substrate) with multiple doses of ribociclib (400 mg) increased [redacted] xposure by 3.8-fold. Co-administration of [redacted](CYP1A2 substrate) with multiple doses of ribociclib (400 mg) increased[redacted] xposure by 20% (1.2-fold). Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index should be avoided. Concurrent use of CYP1A2 substrates is not expected to lead to clinically important drug-drug interactions (DDIs).

Food does not affect the PK of ribociclib administered as a capsule or tablet formulation; therefore ribociclib capsules or tablets can be taken without regard to meals (CLEE011A2111 and CLEE011A2103).

Refer to the ribociclib Investigator's Brochure for additional details.

1.1.4.1.6 Clinical experience with ribociclib in Asian patients based on ongoing clinical trials

The combination of ribociclib (600 mg) with letrozole (2.5 mg once a day) has been evaluated in an ongoing study [CLEE011A2301] involving 51 patients of Asian ethnicity: 28 in the ribociclib + letrozole arm and 23 in the placebo + letrozole arm (Section 1.1.4.1.4). A preliminary analysis of safety and efficacy in the non-Japanese Asian patients compared with the rest of the study population highlighted no substantial differences. Clinically meaningful PFS benefit with ribociclib plus letrozole was maintained in Asian patients (Hazard ratio: 0.378; 95% CI: 0.166-0.906). The combination treatment was well tolerated in Asian patients, with a similar safety profile as observed in the full population (Yap et al 2016).

In addition, a pan-Asian study, CLEE011A2115C, is being conducted to confirm the recommended dose, as well as to provide additional safety and efficacy data for the combination of ribociclib and letrozole when given as first line endocrine therapy for Asian patients with ER+, HER2- advanced breast cancer. At the dose escalation meeting on 13-Jun-2016, the recommended dose of ribociclib was determined as 600 mg in combination with letrozole for Asian non-Japanese patients (patients were from Hong Kong, Singapore, and 1 Chinese patient living in Japan).

There are two other ongoing Phase III trials, which have included Asian patients: MONALEESA-3, ribociclib + fulvestrant in men and postmenopausal women with advanced breast cancer (1st or 2nd line); and MONALEESA-7, ribociclib + tamoxifen/NSAI + goserelin in pre/perimenopausal women with advanced breast cancer (1st line).

The data from the patients enrolled in the MONALEESA-7 (LEE011E2301) study show that there was no major difference in the benefit risk profile of ribociclib between the patients from Asia-selected countries or from Korea with the global population. Pharmacokinetic parameters for ribociclib in combination with letrozole were consistent between Korean, Asian and the global population and did not indicate any ethnic sensitivity. The other factors that could be associated with ethnic sensitivity (such as disease characteristics and medical practice), did not

indicate any differences in the way that ribociclib acts in Asian, and specifically Korean, patients [MONALEESA-7 Ethnic Insensitivity Assessment and Bridging Data Report].

These 2 trials have completed and significant improvement in progression-free survival was observed in these trials. Additional details are provided in Section 1.1.4.1.4.

A MONALEESA-7 subgroup analysis of Asian patients with HR+/HER2-negative ABC found an almost 3-fold improvement in median PFS for patients treated with ribociclib + NASI compared to NASI alone: median PFS was 30.4 months in the ribociclib + NASI arm and 11.0 months in the placebo + NASI arm (HR, 0.470; 95% CI, 0.312-0.706). The Kaplan-Meier estimated overall survival at 36 months was 78.9% in the ribociclib group and 61.5% in the placebo group, a 56% relative reduction in the risk of death with ribociclib was observed. Both ORR and clinical benefit rate (CBR) were improved with the combination of ribociclib and NSAI compared to NASI alone (ORR: 66.2% vs. 36.8%, CBR: 86.2% vs. 63.2%). Adverse events in the Asian subgroup were consistent with the overall population, neutropenia was the only grade 3/4 adverse event observed in 78% of patients treated with ribociclib + NASI. The improvement observed in PFS and overall survival benefit for the Asian population were consistent with the overall NSAI population (Lu et al 2020).

1.1.4.2 Overview of non-steroidal aromatase inhibitors: letrozole and anastrozole

Based on the clinical benefit shown in postmenopausal patients, aromatase inhibitors in combination with ovarian function suppression (OFS), using a GnRH to block the pituitary is usually an effective strategy and have been investigated in premenopausal patients with breast cancer in the (neo)adjuvant, adjuvant and advanced settings. Results from the randomized phase III trials SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial) showed that adjuvant treatment with exemestane + OFS as compared with tamoxifen + OFS, significantly reduced recurrence in premenopausal women with HR+ early breast cancer. Results from both trials (N=5,738) showed statistically significant differences in disease free survival (DFS) at 5 years (91.1% in exemestane + OFS vs 87.3% in tamoxifen + OFS) and rate of freedom from breast cancer at 5 years (92.8% in exemestane + OFS vs 88.8% in tamoxifen + OFS) (Pagani et al 2014). Studies exploring the combination of third generation AIs and goserelin in metastatic premenopausal BC patients are shown below in Table 1-1 (Montagna et al 2013).

Table 1-1 Goserelin and third generation AIs in metastatic premenopausal BC patients

Study	N	AI+goserelin (G)	ORR (CR+PR) (%)	CB (CR+PR+SD) (%)	TTP (months)	First line endocrine therapy
(Forward et al 2004)	16	Anastrozole+G	6.2	75	N/R	No
(Cheung et al 2010)	36 13	Anastrozole+G Exemestane+G*	36 N/R	67 38	12 N/R	Yes No
(Carlson et al 2010)	35	Anastrozole+G	37	72	8.3	Yes
(Park et al 2010)	35	Letrozole+G	46	77	9.5	Yes
(Yao et al 2011)	52	Letrozole+G	21	71	10	Yes/No
(Roche et al 2009)	33	Anastrozole+G	55	64	13	Yes
(Nishimura et al 2012)	37	Anastrozole+G	19	62	7.2	Yes/No

ORR=Objective response rate, CR=Complete response, PR=Partial response, CB=Clinical benefit, SD=Stable disease, PD=Progressive disease, TTP=Time to progression, N/R=Not reported
*In study by Cheung et al 2010, patients received treatment with exemestane after they received treatment with anastrozole.

Although data are limited (Montagna et al 2013), clinical benefit of the combination of AIs and OFS in premenopausal women with advanced ER+ breast cancer has been shown in small phase II studies with letrozole and anastrozole. In one study (Cheung et al 2010), patients received exemestane, but only after they had received anastrozole, so the effect of single–agent exemestane has not been well characterized. Lastly, novel therapeutic approaches targeting promising pathways should be explored to further improve efficacy in premenopausal women with advanced HR+ breast cancer.

1.1.4.3 Overview of Letrozole

Letrozole (Femara®) is a nonsteroidal competitive inhibitor of the aromatase enzyme system with demonstrated efficacy in the treatment of postmenopausal patients with HR+ breast cancer. Letrozole acts by inhibiting in a highly selective fashion the conversion of adrenal androgens to estrogens, which is the primary source of estrogens in postmenopausal women. Letrozole is a highly selective inhibitor of aromatase that induces a 75% to 95% decrease of estrogen levels after two weeks of treatment using daily doses of 0.1 to 5 mg, with no significant clinical and laboratory toxicities or changes in levels of other hormones of the endocrine system as shown in early phase I (Lipton et al 1995; Trunet et al 1996). It is indicated for the adjuvant treatment of postmenopausal women with HR+ early breast cancer as well as the extended adjuvant treatment of patients who have received 5 years of tamoxifen therapy. It is also indicated for the treatment of advanced HR+ breast cancer, both in the first-line setting as well as in patients who have disease progression following anti-estrogen therapy. Letrozole, when given as (neo)adjuvant treatment to women with un-resectable hormone receptor positive early breast cancer, was associated with significantly higher response rate than tamoxifen (60% versus 48%, $p = 0.004$) and a higher percentage of patients underwent breast conservative surgery (48% versus 36%, $p = 0.036$) (Ellis et al 2001).

The most frequently reported adverse events that were significantly different from placebo for letrozole in the adjuvant and extended adjuvant setting include hot flashes, arthralgia/arthritis and myalgia. In the first line setting, the most frequently reported adverse events include musculoskeletal pain (bone/back pain and arthralgia), hot flashes, nausea and dyspnea and incidences of adverse events were similar for tamoxifen in this setting. In general, the observed adverse reactions were mild to moderate in nature.

For information on letrozole and management of letrozole related adverse events refer to the Femara® Prescribing Information.

1.1.4.4 Overview of anastrozole

Anastrozole (Arimidex®) is another selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone. It is also indicated for adjuvant treatment of postmenopausal women with early HR+ breast cancer and first line as well as second line treatment of postmenopausal women with advanced HR+ breast cancer. Current treatment guidelines consider there is no compelling evidence showing meaningful efficacy or toxicity differences between the 3 clinically approved AIs: letrozole, anastrozole and the steroidal AI (exemestane) (Gradishar et al 2017).

The adverse reactions occurring with an incidence of ≥10% in women taking anastrozole included: hot flashes, asthenia, arthritis, pain, arthralgia, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, headache, bone pain, peripheral edema, increased cough, dyspnea, pharyngitis and lymphedema. For information on anastrozole and management of anastrozole related adverse events refer to the Arimidex® Prescribing Information.

1.1.4.5 Overview of Goserelin

Goserelin (Zoladex®) is a synthetic decapeptide analog of gonadotropin releasing hormone (GnRH) indicated for prostatic carcinoma, endometriosis, assisted reproduction, precocious puberty, and advanced breast cancer. Ovarian suppression of estrogen biosynthesis release with goserelin are effective in preventing relapse in premenopausal women with early stage ER+ breast cancer. A meta-analysis of four randomized trials comparing an LHRH analogue alone versus an LHRH analogue plus tamoxifen in premenopausal women with advanced breast cancer showed that the combination treatment was significantly superior to LHRH agonist alone [ORR 29.7 and 38.8%, ($p = 0.03$), median progression-free survival (PFS) was 5.4 and 8.7 months ($p = 0.0003$), and median OS was 2.5 and 2.9 years ($p = 0.02$), respectively] (Klijn et al 2001).

Adverse events occurring in > 20% of women included hot flushes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea and peripheral edema (Zoladex® Prescribing Information).

1.1.4.6 Rationale for the combination of ribociclib with NSAI plus goserelin:

While endocrine therapy is effective in treatment of HR+ advanced breast cancer, approximately 30-50% of patients may not respond to it due to a primary resistance. Overexpression of cyclin D1 is seen in the majority of breast cancers, likely activating the

CDK4/CDK6/E2F axis and promoting endocrine resistance. Therefore, using a CDK4/6 inhibitor to block this activity may enhance efficacy of endocrine treatment strategies (Yu et al 2006). Moreover, many advanced breast cancer patients with initial response to endocrine therapy will acquire secondary resistance to these agents (Bachelot et al 2012; Nichols et al 2015). Co-targeting the ER with other key intracellular proliferation and cell survival signaling pathways, such as mechanisms responsible for cell cycle regulation and progression may enhance first-line endocrine responsiveness of endocrine therapy tumors by preventing or delaying the development of acquired resistance for endocrine treatments. So, with a greater understanding of the biologic pathways, inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6), could potentially overcome or delay resistance to endocrine therapy in hormone receptor-positive/HER2-negative patients with MBC led to approval of ribociclib, in combination with endocrine therapy (Hortobagyi et al 2016; Bartsch 2017; Slamon et al 2018; Tripathy et al 2018).

In addition, the USFDA has recently (July 2018) granted approval for ribociclib combination:

- with an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with HR+, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or
- fulvestrant for the treatment of postmenopausal women with HR+, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

1.1.4.7 Docetaxel

Docetaxel (Taxotere®), a cytotoxic taxane, is an anti-microtubule agent effective in the treatment of patients with breast cancer. The clinical profile of docetaxel as an effective cytotoxic agent in the treatment of metastatic breast cancer is well established (Lyseng-Williamson et al 2005). It is prepared by semi-synthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R, 3S)-N-carboxy-3-phenylisoserine,N-tertbutyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

Docetaxel acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells.

In the US and Europe, docetaxel is currently approved for use in breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and squamous cell carcinoma of head and neck cancer. The most commonly reported adverse events for docetaxel as a single agent are neutropenia (reversible and not cumulative; the median day to nadir was 7 days and the median duration of severe neutropenia [< 500 cells/mm^3] was 7 days), infections, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. The severity of adverse events of docetaxel may be increased when docetaxel is given in combination with other chemotherapeutic agents.

Further information regarding 'docetaxel' can be found at Taxotere® Prescribing Information.

1.1.4.8 Capecitabine

Capecitabine (Xeloda®) is a fluoropyrimidine carbamate with antineoplastic activity, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumor tissues, but also in normal tissues, albeit usually at lower levels (Xeloda® Prescribing Information)

Capecitabine is indicated in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy that included an antracycline. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. The dose of capecitabine approved by the USFDA for patients with locally advanced or metastatic breast cancer is 1,250 mg/m^2 twice daily (bid), given intermittently for 14 days on a 21-day cycle. Capecitabine has a favorable safety profile, with AEs readily managed by dose modification, and it offers the additional benefit of convenient oral dosing. Capecitabine is suitable for long-term administration and generally lacks cumulative toxicity with prolonged use (O'Shaughnessy et al 2012).

As a monotherapy, capecitabine was extensively evaluated in the first line metastatic breast cancer in various phase II and phase III clinical trials. The ORR shown in these studies was in a range of 21 to 30% and PFS was between 2.8 to 7.1 months in patients with metastatic breast cancer unselected for ER status. The two phase III studies were conducted in unselected by ER status patients with metastatic breast cancer. In the ANZBCTG0001 study (N = 323) where patients with first-line mBC unsuited for more intensive chemotherapy were randomized to receive capecitabine monotherapy or cyclophosphamide, methotrexate and 5-fluorouracil (CMF). All patients had to have a relapse-free survival interval for at least 6 months following adjuvant chemotherapy and 80% of patients had received adjuvant endocrine therapy. The primary endpoint PFS was similar between two treatment arms (HR = 0.86; 95% CI: 0.67-1.10). Patients enrolled in the capecitabine arm had a median PFS of 7 months and median OS of 22 months, compared to median PFS of 6 months and OS of 18 months in patients randomized to CMF arm. The OS difference was statistically significant in favor of capecitabine arm (HR=0.72; 95% CI: 0.55-0.94; log-rank $p = 0.02$) (O'Shaughnessy et al 2012). Another randomized Phase III study compared the efficacy and safety of first-line capecitabine with pegylated liposomal doxorubicin (PLD) in patients with mBC (Jäger et al 2010). The primary endpoint of time to progression (TTP) was similar with capecitabine and PLD (median TTP, 7.1 months versus 6.2 months, respectively; HR = 1.21; 95% CI: 0.84-1.75; $p = 0.31$). Capecitabine also had efficacy similar to that of PLD in terms of OS (median OS time, 29.4 months versus 22.4 months, respectively (HR = 1.17; 95% CI: 0.79-1.74; $p = 0.44$).

Robert et al, reported a PFS of 6.2 months in ER-positive HER2 –negative breast cancer patients receiving capecitabine monotherapy (Robert et al 2011).

Diarrhea, hand-foot syndrome (HFS), nausea, vomiting and stomatitis are common adverse reaction attributed to capecitabine treatment. Across the phase II/III breast cancer trials, HFS

and diarrhea were the most frequently reported grade 3 or 4 AEs; alopecia and myelosuppression were rare (O'Shaughnessy et al 2012). Further information regarding capecitabine can be found at Xeloda® Prescribing Information.

1.1.4.9 Paclitaxel

Paclitaxel is a cytotoxic agent with proven antitumor activity in a variety of solid tumors, including breast cancer, ovarian cancer, and lung cancer. Paclitaxel is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5β, 20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. The antitumor activity of paclitaxel is based on tubulin-binding and stabilization of non-functional microtubule bundles, thereby blocking normal mitotic spindle development and subsequent cell division (Ringel et al 1991).

In breast cancer, paclitaxel is used both in combination with other agents and as single agent. A weekly (qw) over a three-weekly (q3w) administration schedule has been shown to be more effective in the metastatic as well as in the adjuvant setting after standard chemotherapy (Seidman et al 2008; Sparano et al 2008). In two large randomized Phase 3 studies the overall toxicity profile was similar between the qw and q3w schedule except for neuropathy (higher in qw arm) while other studies have described a more favorable toxicity profile with the qw administration (Eniu et al 2005).

1.1.4.10 Gemcitabine

Gemcitabine (gemcitabine HCl, 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer)) is a nucleoside analogue that exhibits antitumor activity. Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary.

The cytotoxic effect of gemcitabine is attributed to its active metabolites difluorodeoxycytidine di- and triphosphate (dFdCDP, dFdCTP) into which gemcitabine is converted intracellularly. The dFdCDP inhibits ribonucleotide reductase, thereby decreasing the deoxynucleotide pool available for DNA synthesis; dFdCTP is incorporated into DNA, resulting in DNA strand termination and apoptosis.

Gemcitabine is indicated either as a single agent or in combination with other cytotoxic drugs in a variety of indications including platinum resistant/refractory ovarian cancer, NSCLC, metastatic breast cancer as well as locally advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas.

The most common adverse reactions for the single agent (≥ 20%) are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema (Gemzar prescribing information 2018).

1.1.4.11 Vinorelbine

Vinorelbine (Navelbine®) is a semi-synthetic vinca alkaloid (5'nor-anhydrovinblastine) anti-mitotic chemotherapy drug. Vinorelbine destabilizes the microtubules. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Vinorelbine may also interfere with: 1) amino acid, cyclic

AMP, and glutathione metabolism, 2) calmodulin-dependent Ca++-transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis (Navelbine® prescribing information 2018). In vitro studies showed a selective effect on non-neuronal microtubules, which may explain the decreased neurotoxicity of vinorelbine compared with other vinca alkaloids (Johnson et al 1996).

Vinorelbine is indicated either as a single agent or in combination with other drugs as the first line treatment of stage 3 or 4 non-small cell lung cancer in the USA and in Europe, in addition to the NSCLC, vinorelbine is also indicated for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

The most frequent adverse events associated with vinorelbine include alopecia, nausea, vomiting, neuropathy, neutropenia and leukopenia, venous reactions, and localized dermal necrolysis at the site of intravenous injection. Further information regarding vinorelbine can be found at Navelbine® prescribing information.

1.1.5 Potential for drug-drug interactions

The combinations of ribociclib and a NSAI + goserelin is being evaluated in ongoing clinical trials and the currently available data does not suggests presence of a clinically relevant drug-drug interaction between ribociclib, letrozole and anastrozole (Syed 2017). Data from a clinical trial in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following co-administration of the drugs. Similarly for anastrozole, data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrozole following co-administration of the drugs.

In addition, the metabolism of goserelin is not CYP-mediated; rather hydrolysis of C-terminal amino acids is the major clearance mechanism. Based on the available information, goserelin is not expected to affect the metabolism of nor be affected by co-administered drugs (Zoladex® Prescribing Information).

1.1.6 Endocrine therapy versus chemotherapy:

Recommendation for endocrine therapy versus chemotherapy as first-line treatment of hormone receptor-positive metastatic breast cancer (MBC) is endorsed by the main international guidelines such as ASCO and ESO-ESMO guidelines (Bonotto et al 2017). Endocrine therapy should be used as initial treatment except in cases of immediately life-threatening disease, tumors refractory to endocrine therapy, visceral crisis, or rapid progressive disease that mandate a high response rate treatment. Visceral crisis is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible (Cardoso et al 2017). Treatment recommendations should be based on type of adjuvant treatment, disease-free interval, and organ function (Rugo et al 2016).

The preference of endocrine therapy is also supported by data showing a therapeutic benefit with less toxicity and better quality of life in comparison to chemotherapy. Ten-years (between 2004 to 2014), retrospective, real world data in patients with luminal-like HER2-negative

metastatic breast cancer data, also confirmed that there is no significant difference in terms of survival (i.e. both PFS and OS) for chemotherapy versus endocrine therapy (Bonotto et al 2017).

Historical literature suggests that neither survival nor quality of life (QoL) is improved by treating patients with chemotherapy when endocrine therapy has a reasonable chance of providing disease control (Rugo et al 2016). In the absence of visceral crisis (i.e., immediately life-threatening disease), endocrine therapy appeared to be the treatment of choice for visceral metastases in the same way as it was for non-visceral metastases (Robertson et al 2014).

With respect to the option of combining the chemotherapy with the endocrine therapy, historical data suggest that sequential single-modality treatment is equivalent or preferred to combination therapy, although formal comparisons are weak with respect to clinically important end points including symptom control, PFS, and overall survival (OS). For these reasons, the recommended initial course of treatment for HR-positive MBC is endocrine therapy (Rugo et al 2016).

Practical experience, evidences from the randomized trials, and systematic review of results of published randomized Trials has indicated that combining chemotherapeutic agent are associated with higher response rates and longer progress free survival than single-agent regimens. However, despite these superiorities, combination chemotherapeutic therapy neither improved overall survival nor improved the quality of life. The use of combination therapy often involves compromises with regard to dose and frequency of administration, and these compromises may negate the promise of synergy. Indeed, a combination regimen might impair rather than improve quality of life if it induces toxicity disproportionate to response (Sledge et al 2003). For patients with visceral crisis, symptomatic visceral metastasis with certain tumor load or rapid progression of disease or impending visceral compromise, combination chemotherapy is indicated because high response rate is needed.

1.2 Purpose

A retrospective analysis of prescribing data in the Netherlands (N = 520) showed that one quarter of patients with ER+ breast cancer received chemotherapy as initial palliative treatment; in patients with visceral crisis or multiple metastases, the proportion treated with chemotherapy increased to one third (Lobbezoo et al 2016). In the same study, 20% (71/353) of patients older than 50 received chemotherapy as 1st line treatment, whereas 35% (45/239) of patients younger than 50 received chemotherapy as 1st line treatment. This can be explained by the perception that younger women have a more aggressive disease than older women. It is believed that the rates of first-line chemotherapy prescribed in younger women are likely to be even higher in Asia and Middle East than in Europe. Also, with the current treatment options there are limited data to answer whether first-line therapy for significantly symptomatic HR-positive MBC patients should be chemotherapy or endocrine therapy. All these leads to physicians in many countries to prefer the use chemotherapy over the endocrine therapy, in real-world clinical practice setting. Therefore, women with hormone receptor-positive HER2-negative disease, the question of whether to use chemotherapy or endocrine therapy as first-line treatment MBC remains, to date, partially unresolved.

Now, especially with availability of new therapeutic agent like ribociclib, which demonstrated efficacy in combination as initial endocrine therapy, the question whether to use chemotherapy or endocrine therapy gains more importance for substantiation. The recent results from

MONALEESA-7 data demonstrated that for premenopausal women with ER+/HER2- ABC, median PFS with endocrine therapy was 13 months, which was extended to 2 years with the addition of a CDK4/6 inhibitor (ribociclib) (Tripathy et al 2018). The study also showed that for patients with measurable disease, the response rate of endocrine therapy plus CDK4/6 inhibitor was 51%. Studies which evaluated combination chemotherapy in this patient group have demonstrated a response rate of 35 to 45%. Results from the overall survival demonstrate that the addition of ribociclib to endocrine therapy resulted in significantly longer overall survival than endocrine therapy alone with approximately 29% lower risk of death. This demonstrate that there is a substantial clinical benefit of ribociclib plus endocrine therapy as compared with endocrine therapy alone (Im et al 2019). The recent updated median overall survival was 58.7 months with ribociclib + endocrine therapy and 48.0 months with placebo + endocrine therapy (HR, 0.76; 95% CI, 0.61-0.96), with a 24% relative reduction in the risk of death with ribociclib. It is the longest reported period in HR+/HER2-negative ABC among all Phase III trials in this setting (Tripathy et al 2020). Therefore, the current standard 1st line treatment for premenopausal ER-positive HER2-negative metastatic breast cancer patients who are not associated with a critical clinical condition should be ovarian suppression plus endocrine therapy and ribociclib, rather than of chemotherapy.

Palbociclib, a CKD 4/6 inhibitor, when combined with endocrine treatment and compared with capecitabine in Young-PEARL study, palbociclib demonstrated a longer PFS (20.1 vs. 14.4 months; 95% CI: 0.437 to 0.994) (Park et al 2019). For patients with visceral crisis, or aggressive disease which mandated rapid disease control, combination chemotherapy would be needed according to current guidelines. Although combining multiple chemotherapy agents provided significant clinical benefits by providing the superior time to disease progression, ranging from 6 months to approximately 8 months. The median time to disease progression was 6.1 months in the capecitabine plus docetaxel combination arm and 4.2 months with docetaxel alone (O'Shaughnessy et al 2002). Similarly, the PFS was 5.9 months for gemcitabine plus paclitaxel versus 3.9 months for paclitaxel (Albain et al 2008). For patients who received doxorubicin plus paclitaxel, the estimated median time to progression was 8.3 months, significantly longer than the estimated median of 6.2 months for patients who received 5-fluorouracil, doxorubicin, and cyclophosphamide (Jassem et al 2001). However, in first line setting, four phase III clinical trials consistently demonstrated that CDK4/6 inhibitor plus endocrine therapy could generate a tumor response rate higher than 50% (in measurable lesions), which is higher than what has been reported by most of the chemotherapy regimens in phase III studies. The purpose of this trial is to compare the two treatment modalities in the patients with aggressive disease in HR+/HER2- metastatic pre/peri-menopausal breast cancer setting.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Primary Objective:	Primary Endpoint:	Analysis

To determine whether treatment with NSAI + goserelin+ ribociclib prolongs PFS compared to treatment with combination chemotherapy in premenopausal or perimenopausal women with HR+, HER2 negative locally advanced or metastatic breast cancer.	Progression-free survival is defined as the time from the date of randomization to the date of the first documented progression as per local review and according to RECIST 1.1 or death due to any cause.	Refer to Section 12.4.1
Secondary Objectives:	**Secondary Endpoints:**	
To compare time to treatment failure (TTF) between the two treatment arms.	Time to treatment failure is defined as the time from the date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, change to other anti-cancer therapy, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'.	Refer to Section 12.5.1
To compare 3-month treatment failure rate between the two treatment arms.	Treatment failure rate is defined as the proportion of patients who discontinued the study treatment due to progressive disease, death due to any cause, change to other anti-cancer therapy, or discontinuation due to reasons other than protocol violation or administrative problems.	Refer to Section 12.5.1
To determine whether treatment with NSAI + goserelin + ribociclib increases overall response rate (ORR), clinical benefit rate (CBR), and Time to response (TTR) compared to treatment with combination chemotherapy.	• Overall response rate (ORR) is defined as the proportion of patients whose best overall response is either CR or PR, as per local review and according to RECIST 1.1. • Clinical benefit rate is defined as the proportion of patients with a best overall response of CR, or PR or stable disease, lasting for a duration of at least 24 weeks, as defined by RECIST 1.1. • Time to response is defined as the time from the date of randomization to the first documented response of either CR or PR, which must be subsequently confirmed, as defined by RECIST 1.1.	Refer to Section 12.5.1
To compare the overall survival (OS) between two treatment arms.	Overall survival is defined as the time from the date of randomization to the date of death due to any cause.	Refer to Section 12.5.1
To evaluate the safety of ribociclib in combination with NSAI and goserelin, and combination chemotherapies.	Frequency/severity of adverse events, lab abnormalities.	Refer to Section 12.5.2
To compare patient reported outcomes for health-related quality of life in the two treatment arms.	Change from baseline in the global health status/QOL scale score by using FACT-B questionnaires.	Refer to Section 12.5.3

3 Study design

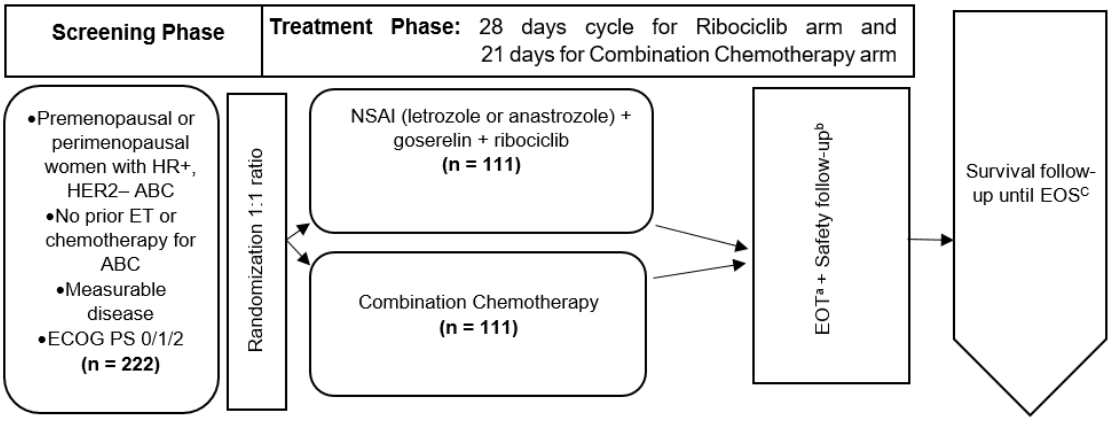
This is a randomized, phase II, open label, multi-center trial comparing the combination of NSAI (letrozole or anastrozole) + goserelin + ribociclib versus combination chemotherapy (either of docetaxel + capecitabine, paclitaxel + gemcitabine or capecitabine + vinorelbine). Premenopausal or perimenopausal women with HR+, HER2-negative, advanced breast cancer with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and fulfill at least one of the following criteria will be considered for this study: symptomatic visceral metastases, or rapid progression of disease or impending visceral compromise, or markedly symptomatic non visceral disease.

Approximately, 222 eligible women patients will be competitively enrolled and randomly assigned to one of the below treatment arms in 1:1 ratio:

- **Ribociclib arm**: NSAI + goserelin + ribociclib (N = 111)
- **Combination chemotherapy arm**: Either of docetaxel + capecitabine, paclitaxel + gemcitabine or capecitabine + vinorelbine based chemotherapy treatment (N = 111). The choice of which chemotherapy combination will be used on study will be decided by the study investigator; once patients' initiate the treatments, switching to another combination chemotherapies will not be allowed.

Randomization will be stratified by (1) the presence of liver metastases (present or absent) (2) DFI <2 years (yes or no, de novo stage 4 is defined as DFI >2 years).

Figure 3-1 Schematic representation of the study design



a. End of treatment (EOT) is defined as until disease progression (radiologically documented according to RECIST 1.1 criteria), unacceptable toxicity, death, or discontinuation from the study treatment for any other reason, including consent withdrawal, patient is lost to follow-up, or the sponsor terminates the study, whichever occurs first.

b. After discontinuation of study treatment, all patients will be followed for safety for 30 days except in case of death, lost to follow-up or withdrawal of consent.

c. Survival follow-up will be done every 16 (± 4) weeks until the EOS, which is defined by the following: at least 46 months from first patient first visit (FPFV) or when required numbers of OS events have been reached (80% of 222 patients have died), whichever occurs first.

Note: Efficacy follow up is through tumor assessment and for FACT-B Questionnaire at every 6 weeks after randomization for the first 12 weeks and every 8 weeks for the next 32 weeks and at every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision.

The study will consist of a 28-day screening phase (after signing the study informed consent form (ICF)), treatment phase (includes EOT visit and safety follow-up) and survival follow up as described in Figure 3-1. Patients will receive study treatment until the following (whichever occurs first): disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason, including consent withdrawal, patient is lost to follow-up, or the sponsor terminates the study.

Patients will be followed for survival regardless of treatment discontinuation for any reason (except if consent is withdrawn, patient is lost to follow-up or until death) and regardless of achieving the primary endpoint, until the deaths, withdrawal of consent, loss to follow-up, or patient/guardian decision. Patients' permanently discontinuing ribociclib, but not any other treatment could remain on study until primary endpoint is achieved.

Discontinuation of the NSAI will necessitate the end of treatment. Patients discontinuing goserelin after at least 1 year of study treatment, which is due to menopausal secondary to oophorectomy or aging, could remain on treatment; however early discontinuation of goserelin will necessitate the end of the treatment.

[redacted]

It is anticipated that patients will be recruited in approximately in 55 sites in 13 countries in approximately 30 months' time.

A Steering Committee has been established, comprising of investigators, Novartis personnel participating in the trial, and one patient, who is not a trial participant to ensure transparent management of the study according to the protocol through recommending and approving modifications as outlined in Section 10.2.2.

3.1.1 Screening phase

Premenopausal or perimenopausal women with HR+, HER2-negative advanced breast cancer will be screened for eligibility within a 28-day screening window prior to starting study treatment on study baseline (Cycle 1 Day 1). During this time, the inclusion and exclusion criteria will be assessed and all screening assessments, laboratory tests, and procedures will be performed. Results of all screening and baseline (Cycle 1, Day 1) evaluations must be reviewed by the investigator or his/her designee prior to patient enrollment into the study in order to assure that all inclusion and exclusion criteria have been satisfied. No re-screening of patients is allowed in this study.

All study patients must be thoroughly informed about all aspects of the study, including the study agents, visit schedule, required evaluations, and all regulatory requirements for informed consent. The signed informed consent must be obtained to participate in this study prior to the performance of any study-related activities. If the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. Eligibility will be determined according to the inclusion/exclusion criteria as described in Section 5. A list of procedures to be performed at the time of screening is summarized in Table 8-1. Patients must meet all eligibility criteria to be considered for enrollment in the study.

3.1.2 Treatment phase

On completion of all screening procedures, patient eligibility will be checked and the eligibility check will be embedded to the Interactive Response Technology (IRT) system. Please refer and comply with detailed guidelines in the IRT manual. Interactive Response Technology system will confirm the inclusion of eligible patients and randomly assign patients to one of the two treatment arms in a 1:1 ratio.

Patients may continue study treatment until the following (whichever occurs first): disease progression (radiologically documented according to RECIST 1.1 criteria), occurrence of unacceptable toxicity, death, or discontinuation from the study treatment for any other reason, including consent withdrawal, patient is lost to follow-up, or the sponsor terminates the study. End of study is defined in Section 3.1.7.

Patients will be followed for survival, at every 16 (± 4) weeks, regardless of treatment discontinuation for any reason (except if consent is withdrawn, patient is lost to follow-up or until death) and regardless of achieving the primary endpoint, until at least 46 months from the first patient first visit (FPFV) date or when required numbers of OS events have been reached (80% of 222 patients have died) (whichever occurs first).

3.1.2.1 Safety and efficacy follow-up

After discontinuation of study treatment, all patients will be followed up for safety for 30 days except in case of death, loss to follow-up or withdrawal of consent. Patients whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first. This could include all study assessments appropriate to monitor the event.

During the safety follow-up, the information of subsequent one line of anti-neoplastic therapy initiated immediately after study treatment discontinuation will be collected.

3.1.3 Survival follow-up

All patients will be followed for survival once they discontinue study treatment and end of efficacy evaluations after at least 46 months from FPFV, or when OS events have been reached (80% of 222 patients have died) (whichever occurs first). Survival follow-up will be conducted every 16 (± 4) weeks or earlier if a survival update is required to meet safety or regulatory needs, after the safety follow-up visit. Survival information can be obtained by clinical visits or telephone calls until death, the patient is lost to follow-up, or the patient withdraws consent for survival follow-up.

3.1.4 Timing of interim analyses and design adaptations

No interim analysis is planned.

3.1.5 Treatment period

Patients will be treated with NSAI + goserelin + ribociclib **or** combination chemotherapies (either docetaxel + capecitabine or paclitaxel + gemcitabine or capecitabine + vinorelbine, as per investigator's choice) until disease progression, unacceptable toxicity, death, withdrawal of consent by the patient, patient is lost to follow up, death, discontinuation from the study treatment due to any other reason or the sponsor terminates the study. For details of assessments, refer to Table 8-1.

3.1.6 Definition of end of treatment

An end of treatment (EOT) will be on the first occurrence of any of the following: disease progression (radiologically documented according to RECIST 1.1 criteria), unacceptable toxicity, death, or discontinuation from the study treatment for any other reason, including consent withdrawal, patient is lost to follow-up, or the sponsor terminates the study.

3.1.7 Definition of end of the study

The end of study will be after 46 months from first patient first visit date or when required number of OS events have been reached (80% of 222 patients have died), whichever occurs first. A End-of-study (EOS) completion eCRF page should be completed at the end of study for every individual patient.

If the primary endpoint, is statistically significant at the primary PFS analysis, data collection will continue during survival follow-up and End of Study will be declared after 46 months from FPFV or 80% of 222 patients have died (whichever occurs first).

If the primary endpoint, PFS, is not statistically significant at the primary PFS analysis then End of Study will be declared and all patients will discontinue all components of study therapy and will complete the safety follow-up period (30 days after EOT visit).

Patients continuing to derive benefit from study treatment at the end of the study in the opinion of the investigator may be transferred to a post-trial access (PTA) following the local country Health Authority regulation(s) and patient's consent, if ribociclib is either not commercially available or not reimbursed to the patients in the country by the time the study is completed. If at the end of the study, patients continuing to derive benefit from comparator treatment in the opinion of the investigator will transitioned onto the commercial available product(s), which should be accessible via their healthcare provider in the respective countries. If the comparator treatment is commercially available but not reimbursed, an alternative option may be discussed between the investigator and Novartis team.

3.1.8 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 9.2 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 boards (IRBs) and/or ethics committees of the early termination of the trial.

4 Rationale

4.1 Rationale for study design

This is a randomized, open label, two-arm study with the objective to compare the effect of combination of NSAI (letrozole or anastrozole) + goserelin+ ribociclib versus combination chemotherapy in premenopausal or perimenopausal patients with advanced breast cancer. The randomized, multi-center, parallel group design is the gold standard design for clinical trials as it minimizes treatment assignment bias, balancing both known and unknown prognostic factors in the assignment of treatments.

A randomization ratio of 1:1 is selected for this phase II trial, which will allow an evaluation of objectives. As in this study treatment blinding cannot be implemented, open-label design is opted.

Randomization will be stratified by the following factors:

1. the presence of liver metastases (present or absent)
2. DFI < 2 years (yes or no).

The stratification factors are selected because of their well-recognized prognostic value.

4.2 Rationale for choice of control drugs or combination drugs

Recent clinical data indicate that inhibitors of CDK4/6 are effective in combination with endocrine therapies in advanced ER+ breast cancer, including in combination with letrozole or

with NSAI (Section 1.1.2). Ovarian suppression of estrogen release with luteinizing hormone-releasing hormone (LHRH) agonists such as goserelin is effective in preventing relapse in premenopausal women with early stage ER+ breast cancer (Klijn et al 2001).

Similarly, the efficacy of chemotherapeutic agent selected in this study are well established in this clinical settings (Section 1.1.4.7 to Section 1.1.4.11).

4.3 Rationale for dose/regimen and duration of treatment

The dose (oral administration of 600 mg daily) and regimen (Days 1-21 of a 28 day cycle) of ribociclib was selected for this study since this dose and regimen were shown to be tolerable and efficacious and approved in several countries worldwide when combined with endocrine therapy in clinical trials in patients with HR+, HER2-negative advanced breast cancer (Section 1.1.4.1.3 and Section 1.1.4.1.4).

The treatment doses will be according to their approved label. Based on available data from preliminary results of patients treated with the combination of ribociclib at 600 mg and letrozole, anastrozole, and goserelin, the combination is tolerable and there is no clinically relevant drug interaction between ribociclib and these above mentioned drugs (Section 1.1.5). Therefore, these doses will be used in this study.

Similarly, in the combination chemotherapies arm, the doses are in accordance with product labeling. The treatment information, including co-therapies are presented in Table 4-1.

Table 4-1 Treatment information

Compound (generic)	Dose and dosage form	Frequency
Ribociclib Arm		
Ribociclib	600 mg (200 mg x 3) Tablets	Days 1-21 of each 28 day cycle
Letrozole (NSAI)	2.5 mg Tablets	Daily (all days of every cycle without interruption).
Anastrozole (NSAI)	1 mg Tablets	Daily (all days of every cycle without interruption)
Goserelin	3.6 mg Subcutaneous implant	Day 1 of each 28 day cycle (an administration window of ± 3 days is allowed)
Combination chemotherapy treatment Arm		
Docetaxel + capecitabine	Docetaxel: 60 - 75 mg/m² on day 1 (IV Infusion)	Docetaxel once, on day 1 of the 3-weeks cycle
	Capecitabine: 1600 - 2500 mg/m²/day (Tablet)	Capecitabine twice daily, on days 1 to 14 of each cycle, followed by a 1-week rest period, in 3 weeks cycle.
Paclitaxel + gemcitabine	Paclitaxel: 175 mg/m^2 (IV Infusion)	Paclitaxel via 3-hour intravenous (IV) infusion on Day 1 in 3-weeks cycles.
	Gemcitabine: 1000 - 1250 mg/m^2 (IV Infusion)	Gemcitabine at via 30-minute IV infusion on Day 1 and Day 8 in 3-weeks cycles

	Paclitaxel: 80 - 90 mg/m^2 (IV Infusion)	Paclitaxel via 1-hour intravenous (IV) infusion on Day 1 and Day 8 in 3-weeks cycles
	Gemcitabine: 800 -1250 mg/m^2 (IV Infusion)	Gemcitabine at via 30-minute IV infusion on Day 1 and Day 8 in 3-weeks cycles
Capecitabine + vinorelbine	Capecitabine: 1600 - 2500 mg/m^2 /day (Tablet)	Capecitabine twice daily on days 1 to 14, followed by a 1-week rest period,, in 3-weeks cycle
	Vinorelbine 60 to 80 mg/m^2/day (oral) or 25 to 30 mg/m^2 (IV infusion)	Vinorelbine, once, on Day 1 and Day 8 in 3-weeks cycles

4.4 Purpose and timing of interim analyses

No interim analysis is planned.

4.5 Risks and benefits

4.5.1 Potential risks to clinical trial participants

The study will be submitted for approval to local Independent Review Boards prior to any patient being enrolled. Patients in this study will be carefully monitored for key toxicities that have been observed with study drugs with periodic laboratory assessment and electrocardiogram (ECG).

Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided for all the investigational drugs in Section 6.5.

A Steering Committee has been established comprising of investigators, Novartis personnel participating in the trial and one patient, who is not participating in this trial to ensure transparent management of the trial according to the protocol through recommending and approving modifications as outlined in Section 10.2.2. A Novartis Safety Management Team periodically reviews and evaluates all emerging data across the ribociclib program for potential safety signal assessment in a timely manner.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study. This study does not cause any risk for the male partners of the female participants.

Risks of imaging procedures

Tumor response will be assessed locally, according to the Novartis guideline version 3.2 (Appendix 2) based on RECIST Version 1.1 (Eisenhauer et al 2009). Imaging assessments will be performed

- at screening within 28 days prior to randomization and

- subsequently at every 6 weeks after randomization/start of treatment for the first 12 weeks and
- at every 8 weeks for the next 32 weeks and
- at every 12 weeks thereafter until progression (radiologically documented according to RECIST 1.1 criteria) or death, withdrawal of consent, loss to follow-up, patient/guardian decision. Please refer to Table 8-1 for details of assessments.

A whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, or FDG-PET) will be performed. If a patient has PET study or whole body bone Magnetic resonance imaging (MRI) within 42 days (6 weeks) before signing informed consent, she do not need an additional bone scan.

Patients will receive radiation when X-ray and computed tomography (CT) scans is done. The radiation received during one examination is the same as 2 - 10 years of normal radiation received in everyday life, depending on the body parts included. Although repeated radiation may damage body tissues and slightly increase the chances of having cancer, however patients should not expect an increased risk from the imaging being done for this study. Patient enrolled in this study are those with aggressive disease status. Therefore, close monitoring of disease status through imaging study is necessary for the safety of the patient.

Patients' visit(s) to study sites for any assessments during public health emergencies, may increase the risk to patients to be impacted by public health issue. In these situations, it will be Principal Investigators' responsibility to make judgments which will be in the best interest of patient's health.

4.5.2 Potential benefits to clinical trial participants

All women patients with HR+/HER2- breast cancer enrolled in this study will receive either ribociclib + NSAI (letrozole or anastrozole) + goserelin or combination chemotherapy (either combination of docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine). The patients in the experimental arm will receive ribociclib in addition to the standard of care NSAI + goserelin. Addition of a ribociclib has already demonstrated clinical benefit without losing the benefit of the back bone therapy. Whereas, the patients in the control arm will receive chemotherapies that are approved and widely used in regular clinical practices for this study indication.

5 Population

The study will include approximately 222 premenopausal or perimenopausal, adult, women with HR+, HER2-negative, advanced breast cancer and have not received neither prior hormonal therapy nor any chemotherapies in advance breast cancer setting. To be considered for this study, the patients must have an advanced disease status that need combination chemotherapy according to PI's judgment. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Patient is an adult female ≥ 18 years old and < 60 years old at the time of informed consent. Written informed consent must be obtained prior to any screening procedures.
2. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer based on the most recently analyzed tissue sample and all tested by local laboratory. ER should be more than 10% ER positive or Allred ≥ 5 by local laboratory testing.
3. Patient has HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing and based on the most recently analyzed tissue sample.
4. Women with inoperable locally advanced or metastatic breast cancer not amenable to curative therapy. Patients must fulfill at least one of the following criteria to be considered that combination chemotherapy is needed according to PI's judgment. However, for patients who are eligible under inoperable locally advanced breast cancer or criteria 4c, the recruitment is stopped to enrich patient population with visceral metastases.
   a. Symptomatic visceral metastases
   b. Rapid progression of disease or impending visceral compromise.
   c. Markedly symptomatic non visceral disease if the treating physician opts to give chemotherapy for rapid palliation of patients' symptoms.
5. Patient is premenopausal or perimenopausal at the time of study entry.
   a. Premenopausal status is defined as either:
      - Patient had last menstrual period within the last 12 months.
        OR
      - If on tamoxifen within the past 14 days, plasma estradiol and FSH are in the premenopausal range, according to local laboratory definition.
      - In case of therapy induced amenorrhea, plasma estradiol and/or FSH are in the premenopausal ranges according to local laboratory definition.
      - Patients who have undergone bilateral oophorectomy are not eligible.
   b. Perimenopausal status is defined as neither premenopausal nor postmenopausal (see exclusion criteria 5)
6. Patients must have not received neither prior hormonal therapy nor chemotherapy for advanced breast cancer, except LHRH agonist. Patients who received ≤ 14 days of tamoxifen or a NSAI (letrozole or anastrozole) with or without LHRH agonist for advanced breast cancer prior to randomization are eligible. Patient must have measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (a lesion at a previously irradiated site may only be counted as a target lesion if there is a clear sign of progression since the irradiation)
7. Patient has an ECOG performance status 0 to 2. For patients with ECOG 2, the poor performance status should be due to breast cancer other than underlying medical disease.
8. Patient has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by local laboratory):
   a. Absolute neutrophil count ≥ 1.5×10^9/L
   b. Platelets ≥ 100×10^9/L

c. Hemoglobin ≥ 9.0 g/dL
d. Estimated glomerular filtration rate ≥ 30 mL/min by a Cockcroft-Gault formula.
e. Total bilirubin < ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN or total bilirubin ≤ 1.5 ULN in patients with liver metastases.
f. Aspartate transaminase (AST) < 2.5 × ULN, except for patients with liver metastasis, who are only included if the AST is < 5 × ULN and Alanine transaminase (ALT) < 2.5 × ULN, except for patients with liver metastases, who are only included if the ALT is < 5 × ULN.

9. Patient must have the following laboratory values within local normal range or corrected to within local normal range with supplements before the first dose of study medication:
   - Potassium
   - Magnesium
   - Total Calcium (corrected for serum albumin)
10. Standard 12-lead ECG values assessed by the local laboratory
    - QTcF interval at screening < 450 msec (QT interval using Fridericia's correction)
    - Mean resting heart rate 50-99 bpm (determined from the ECG)
11. Confirmed negative serum pregnancy test (β-hCG) before starting study treatment or patient has had a hysterectomy.
12. Must be able to swallow investigational tablets or capsules.
13. Patients must be able to communicate with the investigator and comply with the requirements of the study procedures.
14. Must be willing to remain at the clinical site as required by the protocol.

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

1. Patient has received prior systemic anti-cancer therapy (including hormonal therapy and chemotherapy, or any CDK4/6 inhibitor for advanced breast cancer.
   - Patients who received (neo)adjuvant therapy for breast cancer are eligible. If the prior (neo)adjuvant therapy included aromatase inhibitors, the treatment free interval must be greater than 12 months from the completion of aromatase inhibitor treatment until randomization.
   - If patients have disease recurrence during adjuvant tamoxifen treatment, disease free interval (defined as duration between the date of patient received complete tumor resection for primary breast cancer lesion to the date of disease recurrence documented) must be greater than 12 months.
   - Patients who are receiving ≤ 14 days of tamoxifen or NSAI or LHRH agonists ≤ 28 days for advanced breast cancer prior to randomization are eligible.
2. Patient has received extended-field radiotherapy ≤ 2 weeks prior to randomization or limited field radiotherapy ≤ 2 weeks prior to randomization, **and** has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion). Patient

from whom ≥ 25% (Ellis 1961) of the bone marrow has been previously irradiated are also excluded.

3. Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell skin carcinoma, or curatively resected cervical cancer *in situ*.

Note: CNS involvement must be ruled out by assessments if a patient has any signs or symptoms indicating potential CNS metastases.

4. Participation in other studies involving investigational drug(s) within 30 days prior to randomization or within 5-half-lives of the investigational product, (whichever is longer) or participation in any other type of medical research judged not to be scientifically or medically compatible with this study. If the patient is enrolled or planned to be enrolled in another study that does not involve an investigational drug, the agreement of the Novartis study medical lead is required to establish eligibility.
5. Patient is postmenopausal. Postmenopausal status is defined either by:
   - Prior bilateral oophorectomy

   OR
   - Age ≥ 60 years

   OR
   - Age < 60 years and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range.

   Note: For women with therapy-induced amenorrhea, serial measurements of FSH and estradiol serum levels are needed to ensure menopausal status (Denlinger et al 2017).
6. Pregnant or breast-feeding (lactating) women or women who plan to become pregnant or breast-feed during the study
7. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study treatment and for 21 days after stopping the treatment. Highly effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Total hysterectomy or tubal ligation at least 6 weeks before taking study treatment
   - Male partner sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient
   - Placement of an intrauterine device

Note: Use of oral (estrogen and progesterone), transdermal, injected, implanted hormone containing intrauterine systems (IUS) or any other hormonal methods of contraception is not allowed in this study. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

8. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, including any of the following:

- History of documented myocardial infarction, angina pectoris, symptomatic pericarditis, or coronary artery bypass graft within 6 months prior to study entry
- Documented cardiomyopathy
- Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
  - Risk factors for Torsades de Pointe (TdP) including uncorrected hypocalcemia, hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
  - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug)
  - Inability to determine the QTcF interval
  - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
  - Systolic blood pressure >160 or <90 mmHg

9. Patients who have lung metastases with oxygen demand in resting status.
10. Patients who have liver metastases with bilirubin >1.5 ULN.
11. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
    - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment.
    - Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
    - Leptomeningeal metastases is not allowed, even with stable clinical condition.
12. Patient has impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection), as decided by the investigator.
13. Patient has a known history of human immunodeficiency virus (HIV) infection (testing not mandatory).
14. Patient is concurrently using hormone replacement therapy.
15. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol: (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).
16. Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1:

- Concomitant medications, herbal supplements, and/or fruits (e.g. grapefruit, pummelos, star fruit, Seville oranges) and their juices that are strong inducers or inhibitors of CYP3A4/5,
- Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.

17. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects.
18. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.

Note: The following uses of corticosteroids are permitted: a short duration (< 5 days) of systemic corticosteroids; any duration of topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).

19. Patient with a known hypersensitivity to any of the excipients of ribociclib, anastrozole, letrozole, goserelin, the chemotherapy drug that is going to be used, or to any of the other ingredients of the study medication (including peanut and soy).
20. Not able to understand and to comply with study instructions and requirements.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Study treatment

For this study, the terms “investigational drug” refers to Novartis study drug ribociclib (LEE011). The other drugs to be used in this study are letrozole, anastrozole, goserelin, and combination chemotherapies. Goserelin could be substituted by leuprorelin (leuprolide) as requested by the principal investigator with informing the study team before randomization. The combination chemotherapies will be used in this study are either combination of docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine.

Novartis will supply ribociclib (LEE011) as 200 mg tablets as individual patient supply packaged in bottles. All other investigational drugs will be procured locally as they are commercially available drugs according to local practice and regulation and will be labeled as “clinical trial use only” and label will be approved by the local regulatory authorities, if required by country regulation. Storage conditions are described in the medication label. All treatment medications should be used in accordance with the locally approved label. Medication labels will comply with the legal requirements of the country and be printed in the local language. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record Case Report/Record Form (eCRF).

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical dosage form and route of administration	Frequency and/or Regimen	Supply type	Sponsor (global or local)
Ribociclib arm (endocrine treatments)				
Ribociclib (LEE011) 600 mg (200 mg × 3)	Tablets for oral use	Days 1-21 of each 28 day cycle	Open label supply	Sponsor (global)
Letrozole 2.5 mg	Tablets for oral use	Daily (all days of every cycle without interruption).		Sponsor (local)
Anastrozole 1 mg	Tablets for oral use	Daily (all days of every cycle without interruption).		
Goserelin 3.6 mg	Subcutaneous implant	Day 1 of each 28 day cycle (regardless of ribociclib treatment cycle) with an administration window of ± 3 days		
Control arm (combination chemotherapies)				
Docetaxel (60 – 75 mg/m²)/capecitabine (1600 – 2500 mg/m²/day)	Docetaxel: IV Infusion Capecitabine: Tablets for oral use	Docetaxel once, on day 1 of the 3-weeks cycle, Capecitabine twice daily, on Days 1 to 14, followed by a 1-week rest period, in 3 weeks cycle.	Open label supply	Sponsor (local)
Paclitaxel (175 mg/ m^2)/ gemcitabine (1000 - 1250 mg/m^2)	IV infusion	Paclitaxel via 3-hour intravenous (IV) infusion on Day 1 in 3-weeks cycles. Gemcitabine at via 30-minute IV infusion on Day 1 and Day 8 in 3-weeks cycles		
OR				
Paclitaxel (80 - 90 mg/m^2)/ gemcitabine (800 - 1250 mg/m^2)		Paclitaxel via 1-hour intravenous (IV) infusion on Day 1 and Day 8 in 3-weeks cycles.		
		Gemcitabine at via 30-minute IV infusion on Day 1 and Day 8 in 3-weeks cycles		
Capecitabine (1600 - 2500 mg/m^2/day)/ vinorelbine (60 to 80 mg/m^2/day [oral] or (25 to 30 mg/m^2 [IV infusion])	Capecitabine: Tablets for oral use Vinorelbine: Capsule for Oral use/IV infusion	Capecitabine twice daily on day 1 to 14, followed by a 1-week rest period, in 3-weeks cycle		
		Vinorelbine, once, on Day 1 and Day 8 in 3-weeks cycles		

Ribociclib, letrozole, anastrozole and goserelin will be administered as a flat-fixed dose, and not by body weight or body surface area. Whereas, combination chemotherapies (docetaxel + capecitabine, paclitaxel + gemcitabine, capecitabine + vinorelbine) will be administered by body surface area. The dose of study medication will be adapted during the study in case the change (increase or decrease) in body surface area exceeds 10% of the body surface area compared to Visit 2 or the last dose adjustment due to a change in the patient's body surface area. All study treatment drugs must be administered together at approximately the same time (or within few hours for chemotherapy) each day. All oral study treatment drugs can be administered with or without food. Except ribociclib, all study treatment drugs should be used in accordance with the locally approved label. Ribociclib will be used in accordance to protocol guidelines. The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). Patients will be instructed to return unused study drugs to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed.

6.1.2 Treatment arms/group

Patients will be assigned to one of the following 2 treatment arms in a ratio of 1:1:

- **Ribociclib arm**: NSAI + goserelin + ribociclib. Other endocrine therapy should be stopped. Goserelin could be substituted by leuprorelin as requested by PI.
- **Combination chemotherapy arm**: docetaxel + capecitabine, paclitaxel + gemcitabine or capecitabine + vinorelbine based chemotherapy treatment. The chemotherapy regimen will be decided by the treating physician. The patients who will be administered with chemotherapy, will be allowed to receive granulocyte-colony stimulating factor (GCSF) as per treating physician decision, but if patients receive endocrine therapy prior to randomization, endocrine therapy should be stopped.

6.1.3 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial, except bone targeted agents such as bisphosphonate, denosumab, or beta-blocker.

6.1.4 General dosing guidelines

6.1.4.1 Ribociclib treatment arm:

The study treatments should be taken as follows:

- Ribociclib is dosed orally for the first 21 days out of a 28 day cycle.
- Letrozole, or anastrozole are dosed orally daily (28 days out of the 28 day cycle).
- Goserelin is continuously released via a subcutaneous implant injected on Day 1 of each 28 day cycle (regardless of ribociclib treatment cycle) with an administration window of ± 3 days.

For patients who is receiving LHRH agonist before randomization, goserelin is still need to be given on cycle 1 day 1.

- Patients should be instructed to take the study drug combination of ribociclib with a large glass of water (~250 mL or ~8 oz) at the same time each day, patients can

determine if they prefer morning or early afternoon dosing, but should maintain a consistent time. Evening doses are strongly not recommended. In general, ribociclib letrozole or anastrozole tablets may be taken without regard to meals. Please see Section 6.1.5 below for additional guidelines for scheduled visit days.

- Patients receiving ribociclib must avoid consumption of grapefruit, grapefruit hybrids, pomelos/pummelos, star-fruit, Seville oranges or products containing their juice during the entire study and preferably 7 days before the first dose of study medications and during the study, due to potential CYP3A4 interaction with the study medications. These foods are known as CYP3A4 inhibitors and have a potential to increase exposure to ribociclib. Orange juice is allowed.
- Patients should be instructed to swallow the capsules and tablets whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Goserelin implant should be administered as a subcutaneous injection in Day 1 of each 28 day cycle (regardless of ribociclib treatment cycle) with an administration window of ± 3 days using an aseptic technique under the supervision of a physician. Administration technique should be in accordance with the locally approved label (SmPC).
- Herbal or dietary supplements known as strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation are not permitted.
- Multivitamins are permitted.
- All pre-medication given during the study must be recorded on the Concomitant Medication page of the eCRF.
- Other concomitant medication given during the study must be recorded on the Concomitant Medication page of the eCRF.

6.1.4.2 Combination chemotherapies arm

- Docetaxel + capecitabine combination: Docetaxel should be administered at the dose of 60 to 75 mg/m² once on day 1 of the 3-week cycle whereas, the capecitabine should be administered at dose of 1600 to 2500 mg/m²/day twice daily on days 1 to 14.
- Paclitaxel + gemcitabine combination: Paclitaxel should be administered either on Day 1 (at dose of 175 mg/m^2) via an approximately 3 hour infusion, or on Day 1 and 8 (at dose of 80 - 90 mg/m^2) via an approximately 1 hour infusion in each cycle. Gemcitabine at dose of 1000 to 1250 mg/m^2 or 800 to 1250 mg/m^2 dose should be administered via 30 minute infusion on Day 1 and Day 8 in 3-week cycles.
- Capecitabine + vinorelbine combination: Capecitabine should be administered at the dose of 1600 to 2500 mg/m^2/day twice daily days 1 to 14 on a 3-weeks cycle and vinorelbine (either 60 to 80 mg/m^2/day [for oral capsule] or 25 to 30 mg/m^2 [for IV infusion]), once daily, on Day 1 and Day 8 (Note: switch between Vinorelbine oral capsule and Vinorelbine IV infusion is allowed).

- The capecitabine dose (capsule for oral use) must be taken with food or within 30 minutes after a breakfast/meal with approximately 200 ml of water. The vinorelbine tablets could be administered with some food, or after the meal.
- For patients with bilirubin >1 × ULN, the initial dose of docetaxel should be administered at the dose of 30 to 37 mg/m² once on day 1 of the 3 week cycle. For patients with bilirubin level >1.25 × ULN, the initial dose of paclitaxel, could be administered at the dose of 135 mg/m² once on day 1 of the 3 week cycle, or 65 mg/m² on Day 1 and 8 of the 3 week cycle. No need to modify the initial dose of gemcitabine, capecitabine, and vinorelbine based on base line bilirubin level.
- The patients who will be administered with combination chemotherapies, will be allowed to receive GCSF as per treating physician decision.
- Patients who will be administered with oral chemotherapies should be specially instructed to swallow the capsules and tablets whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- No herbal medications-are permitted.
- Multivitamins are permitted.
- All pre-medication given during the study must be recorded on the Concomitant Medication page of the eCRF.
- Other concomitant medication given during the study must be recorded on the Concomitant Medication page of the eCRF.

Paclitaxel pre-medication

Standard pre-medication should be administered according to local practice. The following treatment is recommended (Seidman et al 2008):

- Dexamethasone 10-20 mg or equivalent, one dose before paclitaxel
- Diphenhydramine 50 mg (αH1 receptor), one dose before paclitaxel

Either ranitidine 50 mg or cimetidine 300 mg (H2 receptor), one dose before paclitaxel. Standard premedication treatment should be given 30 to 60 minutes before the paclitaxel infusion or according to local standard of care.

Docetaxel pre-medication

Standard pre-medication should be administered according to local practice. The following treatment is recommended (Taxotere® Prescribing Information):

- Dexamethasone 16 mg per day (e.g., 8 mg twice daily, or other steroid with equivalent potency) for 3 days starting 1 day prior to docetaxel administration.

6.1.5 Additional dosing guidelines for scheduled visit days

On days with fasting, (overnight fasting defined as at least 8-12 hours) biochemistry and/or lipid profile samples as outlined in Table 8-1, the following additional guidelines should be followed:

- The patient must be fasting overnight for all cycle visits for at least 8-12 hours prior to the blood collection for chemistry parameters, and fasting glucose samples. Water is allowed during all fasting periods; however coffee, tea and juice are not permitted during the fasting period. After the fasting blood sample is obtained in the clinic, the patient may consume breakfast, if desired.
- If a pre-dose ECG measurement should be collected, then the ECG measurement should occur before dosing of the study treatment and the information will be recorded in the eCRF.

6.1.6 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to Section 6.5.

During the study, patients in the combination chemotherapy arm should continue to receive chemotherapy until disease progression (radiologically documented according to RECIST 1.1 criteria) or unacceptable toxicity. When one of the combination chemotherapy drugs has to be stopped because of toxicity, the patient may be continued on the other better tolerated chemotherapy drug (monotherapy) (the patients can't switch to another combination chemotherapies). After switching to monotherapy, the patient will be continued with monotherapy for 2 cycles and if the patients does not recover from the toxicity symptom of previous combination chemotherapy, the patient will be continuing with the monotherapy. Patients for whom even the monotherapy has to be stopped because of toxicity are allowed to switch to endocrine therapy, and will be defined as an event for secondary endpoint, time to treatment failure. However, they should not receive the CDK4/6 inhibitor, or switch to a different chemotherapy agent. If patient received CDK4/6 inhibitor, or switch to a different chemotherapy agent without evidence of disease progression, their data will be censored for the primary endpoint, and will be defined as an event for secondary endpoint: time to treatment failure.

Patients in the ribociclib arm will be censored for the primary endpoint, and will be defined as event for secondary endpoint of time to treatment failure if they switch to a different endocrine therapy, or to chemotherapy, unless they have an event (e.g., disease progression). Switching between letrozole or anastrozole (both NSAI) is allowed in case of toxicity related to AI such as arthralgia. Switch goserelin to leuproreline or other LHRH agonists will be allowed after discussion with and approved by study team. Leuprorelin or other LHRH agonists dosing will be as per the local approved label.

6.1.7 Treatment duration

Patients will receive trial treatment until the following (whichever occurs first), disease progression (radiologically documented according to RECIST 1.1 criteria), unacceptable toxicity, death, or discontinuation from the study treatment for any other reason, including consent withdrawal, patient is lost to follow-up, or the sponsor terminates the study. Patients will be followed for survival, at every 16 (± 4) weeks, regardless of treatment discontinuation for any reason (except if consent is withdrawn, patient is lost to follow-up or until death) and

regardless of achieving the primary endpoint, after at least 46 months from first patient first visit (FPFV), or when 80% of OS events have been reached (whichever occurs first). For patients who in the opinion of the investigator are still deriving clinical benefit from study treatment, every effort will be made to continue provision of study treatment. For additional detail, please refer to Section 3.1.7.

6.2 Other treatments

6.2.1 Concomitant therapy

Megestrol acetate and medroxyprogesterone treatment for any reason are not allowed in both arm.

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed. Please consult the list of prohibited medications (Table 16-1) and the list of use with caution medications for further guidance (Table 16-2). The patient must be told to notify the investigational site about any new medications she takes after the start of the study treatment. All medications (other than study drugs), and significant non-drug therapies (including vitamins, herbal medicines, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF. If patients take concomitant medications chronically, any change in dose schedule of concomitant medication throughout the study period should be clearly documented.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If the patient is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

For the ribociclib treatment arm:

The list of prohibited medications and the list of medications that are to be used with caution during combined ribociclib, NSAI, and goserelin treatment are provided, respectively, in Table 16-1 and Table 16-2 in Appendix 1.

This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions. These medications should be excluded if possible. If they must be given based on the investigator's judgment, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time:

- Moderate inhibitors or inducers of CYP3A4/5 (may increase or decrease ribociclib exposure, respectively).
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index (ribociclib may increase exposure to these medications).
- Strong inhibitors of BSEP (based on *in vitro* data co-administration with ribociclib may lead to intrahepatic cholestasis).

- Sensitive substrates of the renal transporters, MATE1 and OCT2 (ribociclib has the potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements).
- Sensitive substrates of transporter BCRP (ribociclib has the potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements).
- Medications that carry a possible risk for QT prolongation (may precipitate QT prolongation and TdP).
- Substrates metabolized predominantly by CYP2C19 or CYP2A6 with a narrow therapeutic index (that could be affected by letrozole).

For the combination chemotherapy arm:

Patients receiving capecitabine

- Oral coumarin-derivate anticoagulants such as warfarin and phenprocoumon should be avoided in patients receiving capecitabine as study treatment. If patient needs to take coumarin-derivate anticoagulants anticoagulant response (INR or prothrombin time) should be monitored frequently in order to adjust the anticoagulant dose based on capecitabine prescribing information. Altered coagulation parameters and / or bleeding, including deaths have been reported during concomitant use.
- Aluminium hydroxide- and magnesium hydroxide-containing antacid (such as Maalox) should not be administrated immediately after capecitabine because of their effect on the pharmacokinetics of capecitabine.
- The level of phenytoin should be carefully monitored in patients receiving capecitabine and phenytoin dose may need to be reduced.
- Care should be also exercised when capecitabine is co-administered with CYP2C9 substrates.

Patients receiving gemcitabine

No specific drug interaction studies have been conducted for gemcitabine. Thus, no recommendations or prohibited concomitant medications are provided in the gemcitabine prescribing information.

Patients receiving docetaxel

In vitro studies have shown that the metabolism of docetaxel may be modified by the, concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as ketoconazole. Caution should be exercised with these drugs when treating patients receiving docetaxel as there is a potential for a significant interaction.

Patients receiving paclitaxel

- Care should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4.

- Care should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Patients receiving vinorelbine

- Administration of vinorelbine to patients with prior or concomitant radiation therapy may result in radiosensitizing effects.
- Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily.

6.2.1.2 Use of bone targeted agents

Bisphosphonates and denosumab are generally allowed with the following comments:

- Adjuvant bisphosphonate/denosumab therapy is allowed as per local and ASCO guidelines.
- Chronic concomitant bisphosphonate/denosumab therapy for the prevention of bone metastasis is not permitted.
- Bisphosphonate/denosumab therapy for the treatment of osteoporosis is permitted.
- Bisphosphonate/denosumab therapy for the prevention of skeletal related events for patients with bone metastases is permitted.
- If bisphosphonate/denosumab therapy is to be started after the first dose of study drug, prior consultation and approval by Novartis is required and the reason for its use must be clearly documented.

Patients taking concomitant medication chronically could be maintained at the same dose, or could be decrease in dose or prolong in dose schedule, and dose schedule throughout the study period, as medically feasible. Increase the dose or shortening the dose schedule is not allowed, unless approved by Novartis after consultation, with the reason documented.

6.2.1.3 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially reducing ribociclib drug exposure to sub-therapeutic levels. Systemic corticosteroid treatment should not be given in ribociclib arm during the study, except for:

- Topical applications (e.g., rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
- A short duration (<5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic).

6.2.1.4 Hematopoietic growth factors

The patients who are enrolled in combination chemotherapy arm will be allowed to receive GCSF as per treating physician decision. Prophylactic use of GCSF with ribociclib is not recommended.

6.2.1.5 Palliative radiotherapy

Palliative radiation is permitted. It should not be delivered to a target lesion. Cumulative courses of RT should not encompass ≥ 25% of the irradiated bone marrow (See Appendix 4). If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

No dose modification of study treatment is mandated during palliative radiotherapy.

6.2.1.6 Use of antiemetic medications

Ribociclib has low to minimal emetogenic potential according to a definition of antineoplastic agent emetogenicity (Grunberg et al 2011). Antiemetic therapy can be used according to clinical guidelines for antineoplastic medications with low to minimal emetogenic potential for treatment and/or prevention of nausea and vomiting as a result of study treatment (NCCN Clinical Practice Guidelines in Oncology, Antiemesis 2016; Roila et al 2016).

Potential drug interaction between ribociclib and antiemetic medications should always be taken into consideration. Example of a prohibited antiemetic medication is ondansetron that in combination with ribociclib may precipitate TdP. Refer to Section 6.2.1 and Section 6.2.2 for a list of medications that are allowed or prohibited to be used with ribociclib.

Antiemetic therapy can be used according to clinical guidelines for patient receiving chemotherapy.

6.2.1.7 Use of beta-blocker

During the screening, if the patients' heat rate is above 100/min, beta-blocker will be allowed. Thereafter, if the patients' heart rate is under control, ECG shows no QT~~cF~~ prolongation and the patient is clinically and hemodynamically stable, they will be allowed to participate in the study.

6.2.2 Prohibited medication

The following medications are prohibited during combined ribociclib, NSAI, and goserelin treatment in this study (Table 16-1 in Appendix 1, this list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions).

- Strong inhibitors or inducers of CYP3A4/5 (may significantly increase or decrease ribociclib exposure, respectively).
- Substrates of CYP3A4/5 with a narrow therapeutic index (ribociclib may increase exposure to these medications resulting in toxicity to these medications).
- Medications with a known risk for QT prolongation and/or TdP (may precipitate QT prolongation and TdP in combination with ribociclib).
- Other investigational and antineoplastic therapies.
- Herbal preparations/medications and dietary supplements that are strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation. These include but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng.

Patients should stop using these preparation/medications at least 7 days prior to first dose of study treatment.

6.2.3 Drugs with QT prolongation

As far as possible, avoid co-administering medications with a "Known", "Possible" or "Conditional" risk of TdP (www.qtdrugs.org) or any other medication with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI increasing the exposure of ribociclib or the exposure of the QT prolonging drug). If concomitant administration of drugs with a known risk of TdP is required and cannot be avoided, ribociclib must be interrupted (please refer to Table 6-5). If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk" of TdP is required, based on the investigator assessment and clinical need, study treatment may be resumed under close clinical and ECG monitoring to ensure patient safety. A list of drugs associated with QT prolongation and/or TdP is available online (www.qtdrugs.org).

Medications with a known risk for QT prolongation are prohibited during study treatment.

6.2.4 Concomitant medications associated with menopausal status

It is important to consider potential drug-drug interactions when using concomitant medications associated with hot flushes and other anticipated symptoms associated with this indication/use of endocrine therapy. Please refer to Table 16-1 in Appendix 1 for further information on prohibited concomitant medications.

6.2.5 Rescue medication

Granulocyte-colony stimulating factor treatment is allowed for patient with neutropenia induced by chemotherapy, or neutropenic fever induced by study drugs in both arms. GCSF treatment is not recommended for patient with neutropenia without infection in patients receive ribociclib treatment. Appropriate treatment for study drug related AEs such as antibiotics for infection should be initiated according to the local guideline and treating physician's decision. When the prohibited medication is definitely needed to be used as a rescue medication for specific clinical situation, the relevant study drug such as ribociclib should be temporarily stop.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient number available.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Patient No. must

not be reused for any other patient and the Patient number for that individual must not be changed. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page. IRT must be notified within 2 days that the patient was not randomized.

6.3.2 Treatment assignment, randomization

Patients will be randomized to one of the two treatment arms in a ratio of 1:1.

Randomization will be stratified by the following factors:

1. the presence of liver metastases (present or absent)
2. disease free interval (defined as duration between the date of patient received complete tumor resection for primary breast cancer lesion to the date of disease recurrence documented) < 2 years (yes or no, de novo stage 4 disease is defined as DFI >2 years)

At Baseline (Cycle 1, Day 1) all eligible patients will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. IRT assigns medication kit numbers (only for ribociclib) in every dispensing visit. The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment will be open to patients, investigator staff, persons performing the assessments, and the Novartis clinical trial team.

6.5 Dose escalation and dose modification

Dose escalation is not applicable in this study, unless it is due to the improvement of hyperbilirubinemia.

6.5.1 Dose modifications - Ribociclib treatment arm

Investigators are permitted to interrupt and/or reduce the ribociclib dose in order to allow patients to continue treatment. Dose modifications should be considered for patients who do not tolerate the protocol-specified dosing schedule for ribociclib or where clinical judgment of the treating physician determines that ribociclib dose interruptions and/or reductions are recommended based on the individual benefit/risk assessment. Dose reductions are not planned for goserelin, or NSAIs. Any changes to the dose or interruption of dosing must be recorded on the Dosage Administration Record eCRF. All patients will be followed for adverse events and for serious adverse events for 30 days following the last dose of study drug.

6.5.1.1 Ribociclib

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of ribociclib therapy. Refer to Table 6-2 for guidance. No dose re-escalation is permitted.

Table 6-2 Dose modification guideline-Ribociclib

	Dose	Number of Tablets & strength
Starting dose	600 mg	3 × 200 mg Tablets
First dose reduction	400 mg	2 × 200 mg Tablets
Second dose reduction	200 mg	1 × 200 mg Tablets

Recommendations for dose reduction, interruption or discontinuation of ribociclib in the management of adverse reactions are summarized in Table 6-3, Table 6-4, Table 6-5, and Table 6-6.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. However, for events requiring a discontinuation in Table 6-3, Table 6-4, Table 6-5, and Table 6-6 or listed in Section 9.2, treatment must be discontinued. If dosing was interrupted for >28 days due to ribociclib-related toxicity, ribociclib must be discontinued.

If a patient inadvertently doses on a rest day (e.g., days 22 to 28 of any given cycle), ribociclib will be interrupted to ensure 7 consecutive rest days and avoid overdose. The visit schedule will be adjusted accordingly.

6.5.1.1.1 Recommendations on adjustment of ribociclib treatment cycles in the case of dose interruptions/re-initiation

Delayed start of a cycle:

In the case of ribociclib being withheld at Cycle (x) D1 based on investigator's judgement, the patient should reinitiate ribociclib on a 3 week ON/ 1 week OFF schedule once the assessment(s) are within acceptable levels according to Section 6.5.1. The visit schedule should be adjusted based on the ribociclib treatment schedule.

Mid-cycle dose interruption:

In the case of ribociclib being withheld for <7 days during any cycle, patient should reinitiate ribociclib to complete the 21 calendar day treatment (3 weeks ON) followed by 1 week OFF schedule.

In the case of ribociclib being withheld for ≥ 7 days during any cycle, patient should reinitiate ribociclib to a new 28 calendar day treatment schedule (3 weeks ON/ 1 week OFF) once the assessment(s) are within acceptable levels according to Section 6.5.1. The visit schedule should be adjusted based on the ribociclib treatment schedule.

Table 6-3 Ribociclib dose adjustment and management recommendations for hematological adverse reactions

Toxicity/Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	
Grade 1(≥ 75 × 10^9/L)	No dose adjustment required.
Grade 2 (≥ 50 × 10^9/L – <75 × 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose.
Grade 3 (≥ 25 × 10^9/L - <50 × 10^9/L)	• Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose level. • If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib to the next lower dose level.
Grade 4(<25 × 10^9/L)	• Dose interruption until recovery to grade ≤1. • Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib
Absolute neutrophil count (ANC)	
Grade 1 (≥1.5 × 10^9/L)	No dose adjustment required.
Grade 2 (≥1.0 - <1.5 × 10^9/L)	No dose adjustment required.
Grade 3 (≥0.5 - <1.0 × 10^9/L)	• Dose interruption until recovery to ≥1.0 × 10^9/L. Re-initiate ribociclib at the same dose level. • If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥ 1.0 × 10^9/L. • If resolved in ≤ 7 days, then maintain dose level. • If resolved in >7 days, then reduce ribociclib dose to the next lower dose level.
Grade 4 (<0.5 × 10^9/L)	Dose interruption until recovery to ≥ 1.0 × 10^9/L. Re-initiate ribociclib at the next lower dose level.
Febrile neutropenia	
Grade 3 ANC <1.0 × 10^9/L with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than one hour	Dose interruption until improvement of ANC ≥ 1.0 × 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.
Anemia (Hemoglobin)	
Grade 1 (≥ 10.0 – LLN g/dL)	No dose adjustment required.
Grade 2 (≥ 8.0 – <10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	Dose interruption until recovery to grade ≤ 2. Re-initiate ribociclib at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

Table 6-4 Ribociclib dose adjustment and management recommendations for hepatic toxicities (CTCAE v4.03)

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (>ULN – 1.5 × ULN) (confirmed 48-72h later)	Maintain dose level with LFTs monitored every two weeks
Grade 2 (>1.5 – 3.0 × ULN)	• Dose interruption of ribociclib • If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level • If resolved to ≤ grade 1 in >21-28 days or toxicity recurs, then reduce 1 dose level • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If toxicity recurs after two dose reductions, or recovery to ≤ grade 1 is >28 days, discontinue ribociclib
Grade 3 (>3.0 – 10.0 × ULN)	• Dose interruption of ribociclib, until resolved to ≤ grade 1, then lower 1 dose level of ribociclib • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If resolved to ≤ grade 1 in >28 days or toxicity recurs, discontinue ribociclib
Grade 4 (>10.0 × ULN)	Discontinue ribociclib

Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of liver metastases, evidence of obstruction, such as elevated ALP and GGT typical of gallbladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 × ULN) due to hemolysis or Gilbert Syndrome, other pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs.

For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
AST or ALT	
AST or ALT without bilirubin elevation > 2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 – 72 h later)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or every two weeks in case of increase from baseline grade 0 to 1
Increase from baseline grade 0 or 1 to grade 2 (>3.0 – 5.0 × ULN)	• Dose interruption of ribociclib • If resolved to ≤ baseline grade in ≤ 21 days, then maintain dose level • If resolved to ≤ baseline grade in >21 days or toxicity recurs, then reduce 1 dose level • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is >28 days, discontinue ribociclib
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 × ULN)	• Dose interruption of ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If recovery to ≤ baseline grade is > 28 days, discontinue ribociclib • If toxicity recurs, discontinue ribociclib
Increase from baseline grade 2 to grade 3 (> 5.0 – 20.0 × ULN)	• Dose interruption of ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib.
Grade 4 (>20.0 × ULN)	• Discontinue ribociclib
AST or ALT and concurrent Bilirubin	
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT >3.0 × ULN combined with total bilirubin >2 × ULN without evidence of cholestasis Or For patient with elevated AST or ALT or total bilirubin at baseline: [AST or ALT >2 × baseline AND >3.0 × ULN] OR [AST or ALT 8.0 x ULN] whichever is lower- combined with [total bilirubin > 2 × baseline AND >2.0 × ULN]	• Discontinue ribociclib

Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.

6.5.1.1.2 Additional follow-up for hepatic toxicities

Increase in transaminases combined with total bilirubin (TBIL) increase may be indicative of drug-induced liver injury (DILI), and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT >3.0 × ULN combined with TBIL >2.0 × ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT >2 × baseline AND >3.0 × ULN] OR [AST or ALT >8.0 × ULN], whichever is lower, combined with [TBIL >2 × baseline AND >2.0 × ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation >2.0 × ULN with R value <2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R >2$ and <5) liver injury. In the absence of cholestasis, these patients must be immediately discontinued from study drug treatment, and repeat Liver Function Tests as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin, direct and indirect bilirubin, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), creatine kinase, prothrombin time (PT) or INR and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

Close observation is recommended in case of AST, ALT, and/or bilirubin increase requiring dose interruption, which involves:

- Repeating liver enzyme and serum bilirubin tests **two or three times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases, including history of any pre-existing liver conditions or risk factors.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.
- Considering a liver biopsy, as clinically indicated to assess pathological change and degree of potential liver injury.

All cases of DILI confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant", thus meeting the definition of SAE (Section 10.1.3), and must be reported as SAE using the term "potential drug-induced liver injury". All events must be followed up with the outcome clearly documented. Results of tests as well as other clinically important information will be recorded in the eCRF.

6.5.1.1.3 Additional follow-up for QTc prolongation

Table 6-5 Ribociclib dose adjustment and management recommendations for QTcF prolongation (CTCAE v4.03)

Grade	Dose Modification
For All Grades	1. Check the quality of the ECG and the QT value and repeat if needed. 2. Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib.
1 QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades". No dose adjustment required.
2 QTcF 481-500 ms	1. Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." 2. Perform a repeat ECG within one hour of the first QTcF of ≥ 481 ms. Repeat ECG as clinically indicated until the QTcF returns to < 481ms, restart LEE011 with dose reduced by 1 dose level. Refer to table 6.2 for dosing schedule. 3. If QTcF ≥ 481 ms recurs, ribociclib should be reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. 4. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms
3 QTcF ≥ 501 ms on at least two separate ECGs	1. Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." 2. Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. 3. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms. 4. If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. 5. If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. 6. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms 7. If QTcF of ≥ 501 ms recurs, discontinue ribociclib.
4 [QT/QTcF ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	1. Discontinue ribociclib. Perform steps 1-4 as directed in "For All Grades." 2. Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.

6.5.1.1.4 Additional follow-up for interstitial lung disease/pneumonitis

To minimize the risk of ILD/pneumonitis, monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who develop Grade 1 ILD/Pneumonitis, no dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. In patients who developed ILD/Pneumonitis Grade 2, dose should be interrupted until recovery to Grade ≤ 1, and then ribociclib can be resumed at the next

lower dose level. For Grade 3 or 4 permanently discontinue ribociclib. An individualized benefit-risk assessment should be performed before resuming ribociclib.

6.5.1.1.5 Guidance for all other adverse reactions

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions, if indicated. If electrolyte values are outside of the normal range, interrupt ribociclib administration, correct electrolytes with supplements or appropriate therapy as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes. For all other adverse events, including Toxic Epidermal Necrolysis (TEN), which is a grade 4 event by CTCAE, please follow recommendations in Table 6-6.

Table 6-6 Ribociclib dose adjustment and management recommendation for all other adverse reactions

Grade	Dose Adjustment and Management Recommendations
1	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
2	Dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the same dose. If the same toxicity recurs at grade 2, interrupt ribociclib until recovery to grade ≤ 1. Re-initiate ribociclib at the next lower dose level.
3	Dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤ 1 and reduce ribociclib dose the next lower dose level. If toxicity recurs at grade 3, discontinue ribociclib.
4	Discontinue ribociclib and treat with appropriate medical therapy.

6.5.1.2 Non-steroidal aromatase inhibitors

The established clinical dose of letrozole (2.5 mg/day) and anastrozole (1 mg/day) will be used and no dose modification of letrozole or anastrozole is planned in this study. For information on NSAIs (letrozole or anastrozole) and management of related adverse events refer to the Femara® Prescribing Information or Arimidex® Prescribing Information.

6.5.1.3 Goserelin

The established clinical dose of goserelin (3.6 mg subcutaneous injection on Day 1 of each 28 day cycle with an administration window of ± 3 days) will be used and no dose modification of goserelin is planned in this study. For information on goserelin and management of goserelin related adverse events refer to the Zoladex® Prescribing Information.

6.5.2 Adjustment of starting dose in special populations - Renal impairment for Ribociclib treatment arm

Insufficient data are available to provide a dosage recommendation for ribociclib in patients with renal impairment. A study in non-cancer patients with varying degrees of renal impairment and matched patients with normal renal function is ongoing (CLEE011A2116). Refer to [Ribociclib Investigators Brochure] for more details. Based on rat ADME data, ribociclib was predominantly excreted in the in the bile as metabolites, with limited excretion of unchanged drug in urine.

Studies with goserelin in female patients with renal impairment do not indicate a need for dose adjustment with the use of the depot formulation (Zoladex® Prescribing Information).

Renal impairment does not affect letrozole or anastrozole PK in humans (Femara® Prescribing Information, Arimidex® Prescribing Information).

Patients with baseline renal impairment or with AST/ALT or bilirubin values beyond certain thresholds as specified in the eligibility criteria are excluded from the study. Patients who experience renal impairment (not due to other contributing factors) of grade 2 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

6.5.3 Dose modifications – combination chemotherapies arm

Any changes to the dose or interruption of dosing must be recorded on the Dosage Administration Record eCRF. All patients will be followed for adverse events and for serious adverse events for 30 days following the last dose of study drug. Deviation of the dose modification/discontinuation from the protocol recommendation is allowed only if the benefit of deviation outweighs the risk as judged by PI, and appropriate prophylaxis management is incorporated into next cycle of treatment. Documentation of the judgment is needed before starting the treatment deviated from the protocol recommendation.

6.5.3.1 Paclitaxel

Guidelines for dose modification and dose interruption of paclitaxel are described in Table 6-7 below.

Table 6-7 Dose modifications for suspected toxicities related to paclitaxel

Toxicity	Grade	Actions
Non-hematological	1 or 2	- Continue paclitaxel therapy
	3 or 4 (excluding alopecia and fatigue)	- Delay paclitaxel until toxicity improves to grade ≤ 1 - Restart paclitaxel at 20% reduced dose - If toxicity requires more than 3 weeks from last planned administration to improve to grade ≤ 1, discontinue paclitaxel
Hematological	1 or 2	- Continue paclitaxel therapy
Hematological - ANC ≤ 1.0 × 10^9/L (1,000/mm^3) - Platelets ≤ 50 × 10^9/L (75,000/mm^3) - Hemoglobin ≤ 8.0 g/Dl despite transfusion	3 or 4	- Delay paclitaxel treatment until neutrophils ≥ 1.5 ×10^9/L (1,500/mm^3), platelets ≥ 100 ×10^9/L (100,000/mm^3) and Hgb ≥ 9 g/dL - If recovery occurs ≤ 7 days restart at same dose and schedule - If recovery requires >7 days reduce paclitaxel dose by 20% - If toxicity requires more than 3 weeks from last planned administration to improve to grade ≤ 1, discontinue paclitaxel
Bilirubin, cre, AST, and ALT	1 or 2 (see below for bilirubin and renal function)	- Continue paclitaxel therapy
	3 or 4 (or for bilirubin or creatinine ≥ 2 × ULN; or calculated Cr clearance ≤ 40 Ml/min)	- Delay paclitaxel treatment until toxicity improves to grade ≤ 1 - Restart paclitaxel at same dose - If toxicity recurs reduce paclitaxel dose by 20% - If toxicity requires more than 3 weeks from last planned administration to improve to grade ≤ 1, discontinue paclitaxel treatment

6.5.3.2 Docetaxel

Guidelines for dose modification and dose interruption of docetaxel are described in Table 6-8 below.

Any dose reduction or dose delay of chemotherapy is based upon the severity of a toxicity, as graded by NCI Clinical Toxicity Criteria (NCI-CTCAE, version 4.03). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycles. Re-challenging the patient with docetaxel chemotherapy subsequent to study drug maintenance treatment initiation with study drug will not be allowed.

Blood tests may be performed weekly, as per the local practice and standard of care, to assess in the first cycle of chemotherapy if study treatment can begin. Please refer to Table 6-8 for recommended docetaxel dose adjustments. Hematological testing may be performed on Day 10 (± 3 days) of each cycle to establish the nadir values and to avoid the re-occurrence of any grade 3-4 neutropenia or febrile neutropenia. Dose delays or reductions to docetaxel will be implemented based on these values AND/OR the Day 1 values at the start of each cycle (Table 6-8).

Table 6-8 Criteria for cycle delay and/or dose reductions of docetaxel

RECOMMENDED DOCETAXEL DOSE MODIFICATIONS[1]	
Worst Toxicity CTCAE Grade* (Value)	**DOCETAXEL**
HEMATOLOGIC	
Neutropenia (ANC) – Grade 4 (ANC <0.5 × 10^9/L) for more than one week	Delay treatment until resolution or toxicity returns to Grade 1, then administer reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence
Febrile neutropenia – (ANC < 1.0 × 10^9/L and fever ≥ 38.5°C) for more than one week	Delay treatment until resolution, then administer reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence
Platelets – Grade 4 (<25.0 × 10^9/L)	Delay treatment until resolution, then administer reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence
METABOLIC/LABORATORY	
Alkaline phosphatase – Grade 3 (> 5.0 - 20.0 × ULN)	Delay treatment until resolution, then reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence
Alkaline phosphatase – Grade 4 (>20.0 × ULN)	All sites: Permanently discontinue docetaxel[2]
ALT/SGPT – Grade 3 (>5.0 – 20.0 × ULN)	Delay treatment until resolution, then administer reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence
ALT/SGPT – Grade 4 (>20.0 × ULN)	All sites: Permanently discontinue docetaxel[2]
AST/SGOT – Grade 3 (> 5.0 - 20.0 × ULN)	Delay treatment until resolution, then administer reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence
AST/SGOT – Grade 4 (> 20.0 × ULN)	All sites: Permanently discontinue docetaxel[2]
Bilirubin – Grade 3 (>3.0 – 10.0 × ULN)	Delay treatment until resolution, then administer reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence
Bilirubin – Grade 4 (>10.0 × ULN)	All sites: Permanently discontinue docetaxel[2]
Skin	
Severe or cumulative cutaneous reactions	Delay treatment until resolution or toxicity returns to Grade 1, then administer reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence
Peripheral Nervous System	
Peripheral neuropathy Grade 3 or 4	All sites: Permanently discontinue docetaxel[2]
ALL OTHER non-hematologic ADVERSE EVENTS	
Grade 3 or 4	Delay treatment until resolution or toxicity returns to Grade 1, then administer reduced dose by 20% for 1st occurrence, discontinue docetaxel[2] at 2nd occurrence

[1] Docetaxel dose reduction from 75 mg/m^2 to 60 mg/m^2 is based on the following published studies Chen et al. 2006 and Shim et al 2005.

[2] If study treatment is stopped due to toxicity attributed specifically to docetaxel, the patient may continue to receive study drug as maintenance treatment until documented disease progression, unacceptable toxicity occurs or consent is withdrawn. Maintenance treatment with study drug can commence once docetaxel related toxicities have resolved at the next scheduled cycle visit. Docetaxel chemotherapy will not be administered during maintenance treatment in this study. Re-challenging the patient with docetaxel chemotherapy subsequent to study drug maintenance treatment initiation will not be allowed.

*Common Toxicity Criteria for Adverse Events (NCI-CTCAE Version 4.03).

Hepatic Impairment

Patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN should not receive docetaxel.

6.5.3.3 Gemcitabine

For gemcitabine dose modifications/reductions, dosage adjustment will be based on the degree of hematological toxicity experienced by the patient (Table 6-9). Patients receiving gemcitabine should be monitored, as per the local practice and standard of care, prior to each dose with a complete blood count, including differential and platelet count. If marrow suppression is detected, treatment should be modified or suspended according to the guidelines below:

Table 6-9 Gemcitabine dosage reduction guidelines

Treatment Day	Absolute granulocyte count ($\times 10^6$/L)	Platelet count ($\times 10^6$/L)	% of full dose
Day 1	≥ 1500	and ≥ 100,000	100%
	less than 1500	or less than 100,000	Hold
Day 8	≥ 1200	>75,000	100%
	1000-1199	50,000-75,000	75%
	700-999	≥ 50,000	50%
	<700	<50,000	Hold

For non-hemorrhagic adverse events, gemcitabine should be permanently discontinued for unexplained dyspnea or other evidence of severe pulmonary toxicity, severe hepatic toxicity, hemolytic-uremic syndrome, capillary leak syndrome, and posterior reversible encephalopathy syndrome, Withhold gemcitabine or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved.

6.5.3.4 Capecitabine

Local label should be used for capecitabine dose modifications for the management of adverse reactions or as described in Table 6-10.

Table 6-10 Recommended dose modifications of capecitabine for both hematological and non-hematological toxicity

Toxicity NCIC Grades*	Grade 1		Grade 2		Grade 3		Grade 4	
	During a course of therapy	**Dose adjustment for next treatment (% of starting dose)**	**During a course of therapy**	**Dose adjustment for next treatment (% of starting dose)**	**During a course of therapy**	**Dose adjustment for next treatment (% of starting dose)**	**During a course of therapy**	**Dose adjustment for next treatment (% of starting dose)**
1st appearance	Maintain dose level.	Maintain dose level.	Interrupt until resolved to grade 0-1.	100%	Interrupt until resolved to grade 0-1.	75%	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1.	50%
2nd appearance		-		75%		50%	Discontinue permanently	-
3rd appearance		-		50	Discontinue permanently.	-		-
4th appearance		–	Discontinue treatment permanently.	-		-		-

* Common Terminology Criteria for adverse events v4.0 or toxicity management per local label was used, except for the hand-and-foot syndrome

6.5.3.4.1 Adjustment of starting dose in special populations

Renal impairment

No adjustment to the starting dose of capecitabine is recommended in patients with mild renal impairment (creatinine clearance = 51 to 80 mL/min [Cockroft and Gault, as shown below]). In patients with moderate renal impairment (baseline creatinine clearance = 30 to 50 mL/min), a dose reduction to 75% of the capecitabine starting dose is recommended. Subsequent dose reduction should be made if grade 2 to 4 adverse events occurred, Table 6-10.

Cockroft and Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 × male value

Severe renal impairment

Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min by Cockroft and Gault equation.

Hepatic impairment due to liver metastasis

Patients with mild or moderate hepatic impairment due to liver metastasis should be monitored carefully while administered capecitabine. No starting dose reduction is necessary.

6.5.3.5 Vinorelbine

Hematologic toxicity:

Complete blood counts, as per the local practice and standard of care, will be obtained to assess for hematologic toxicity. Dose modifications may be made on the basis of the blood counts on the day of the scheduled treatment.

On Day 1 vinorelbine will be administered as long as absolute granulocyte count is $\geq 1.5 \times 10^9$/L and platelets are $> 100.0 \times 10^9$/L. If these treatment parameters are not met treatment will be delayed 1 week. If recovery takes >2 weeks, the patient will be discontinued from vinorelbine treatment, but not from the study entirely. On Day 8 the parameters in Table 6-11 will apply:

Table 6-11 Absolute granulocyte and platelet count parameters (Days 8)

Absolute Granulocyte Count ($\times 10^9$/L)	Platelet count ($\times 10^9$/L)	Dose of Vinorelbine
>1.5	>100.0	Full dose
1.0-1.499	75.0 -99.0	15 mg/m^2
<1.0	<75.0	Hold

Peripheral neuropathy (sensory or motor) toxicity:

- Grade 0-1: No Change

- Grade 2-4: Hold therapy and re-evaluate weekly; resume at 15 mg/m^2 for all subsequent treatment when toxicities have resolved or improved to an acceptable level.

Patients who experience Grade 2 or greater neurological toxicity should have vinorelbine held until symptoms are Grade 0-1.

Other non-hematologic toxicities:

For other Grade 3 and 4 toxicities, treatment should be held until the toxicity resolves to baseline or an acceptable level, then reinstituted (if medically appropriate) at the next lower dose level. If treatment is withheld for longer than 2 weeks, the patient will be discontinued from vinorelbine treatment, but not from the study entirely.

Hepatic insufficiency:

1. Total serum bilirubin 2.1 to 3 mg/dL: Give 50% of starting dosage
2. Total serum bilirubin greater than 3 mg/dL: Give 25% of starting dosage
3. Hepatic impairment with concomitant neutropenia: Give the lowest suggested dose adjustment for given degree of neutropenia or hepatic impairment.

6.5.4 Follow-up for toxicities

Patients who complete treatment or whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event. All patients will be followed up for safety for 30 days following the last dose of study treatment.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form and site source document. This information must be captured in the source document at each patient visit. Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee.

6.6.2 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group, third party, and investigational site as appropriate. Study drug destruction at the investigational site will only be permitted, if permitted by local regulations.

6.7 Preparation and dispensation

Patients, enrolled in the ribociclib arm, will be provided with an adequate supply of study drugs for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive ribociclib on an outpatient basis. The investigator shall provide the patient with instructions for ribociclib administration according to the protocol. For the patients assigned to receive chemotherapies as IV infusions, infusions will be prepared by a site pharmacists. If the patients are assigned to receive the chemotherapies orally (as tablets

and capsules), site pharmacists or designee will provide an adequate supply of the study drugs to the patients, including instructions for administration, until at least their next scheduled study visit. Letrozole, anastrozole, goserelin and chemotherapies combinations (capecitabine + vinorelbine, paclitaxel + gemcitabine, and docetaxel +capecitabine) should be dispensed as mentioned in Section 6.1.1. The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT (applicable for patients in the ribociclib arm only) and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit.

- **Ribociclib:** The dispatch of ribociclib from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1 month supply until Cycle 11 and 3 months supply thereafter. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.
- **For other study drugs (letrozole/anastrozole):** Access to these drugs through a pharmacy outside of study site should be ensured by investigator or his/her team. If these are prescription only drugs in the country, investigator may consider sending prescriptions over the email to the patient or patient's relative.
- **For goserelin/leuprorelin:** Procedure for subcutaneous implant for these drugs can be performed by another medical professionals outside of study site. Detailed treatment plan (dose, schedule) should be transferred to the other breast cancer treating physician by principal investigator. The process for assuring oversight of the same including communication to confirm patients' safety and any treatment should be documented.
- **Patients receiving oral chemotherapy drugs:** Prescription delivery to such patients can be arranged or prescription can be issued from another qualified breast cancer treating physician or medical oncologists authorized by the principal investigator. All details should be transferred for the chemotherapy treatment (dose, schedule) to the qualified physician outside study site, and process for assuring oversight should be documented. In addition, any certified source documents (including any other medication records) should be retrieved and maintained in patients' medical record or charts at study site.

- **For patients who are receiving intravenous chemotherapy drugs:** In these cases, patient is not able to self-administer the drug. Risk-benefit of the patient coming to the facility before conducting the on-site visit should be assessed & documented during public health emergencies situation. If on-site visit is not possible and the administration of the intravenous chemotherapy is necessary per patient's overall health status, it may be performed by another qualified breast cancer treating physician or medical oncologists authorized by principal investigator. All details about the chemotherapy treatment (dose, schedule) to this qualified physician outside study site should be transferred by principal investigator. The process for assuring investigator oversight, including communication to confirm patients' safety and any treatment should be documented. In addition, any certified source documents (including any other medication records) should be retrieved and maintained in patients' medical record or charts at study site.

If patient is not able to continue chemotherapy drugs (IV/Oral) due to public health emergencies situations, then principal investigator should imply his/her best clinical judgement while evaluating patient and make the decisions related to continuation of patient in the study.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Ribociclib will be supplied centrally by Novartis and the other study medications (letrozole, anastrozole, goserelin, capecitabine, vinorelbine, paclitaxel, gemcitabine, and docetaxel) will be sourced locally. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the [Investigator's Brochure]. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log, and site source document. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

Table 6-12 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Ribociclib	tablets in bottles	Labeled as 'Ribociclib 200 mg' Study treatment packaging has a 2-part label.

Study treatments	Packaging	Labeling (and dosing frequency)
Anastrozole Letrozole Goserelin Docetaxel Paclitaxel Gemcitabine Vinorelbine Capecitabine	Refer to local product information	Refer to local product information

6.7.1.2 Handling of additional treatment

No other treatment beyond investigational drug and control drug are included in this trial.

6.7.2 Instruction for prescribing and taking study treatment

Details have been provided in Section 6.1.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/ independent ethics committee (IEC)-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority. However signing of ICF should be completed at the study site after informed consent discussion has been conducted and patient agrees to participate in the study.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the ribociclib can be found in the IB. For the other investigational drugs, information about other common side effects can be found in respective product's approved label. This information will be included in the patient

informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

Table 8-1 lists all of the assessments and indicates with an "x", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column). Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

Patients who prematurely discontinue the study for any reason should be scheduled for the EOT, followed by safety follow-up and survival follow up visits and all of the assessments listed in Table 8-1 will be performed. At these visits, dispensed investigational product should be reconciled, and the adverse event and concomitant medications will be recorded on the CRF.

Allowed visit windows are specified as follows:

- Patients meeting all entry criteria will be randomized and will be administered the first dose of study treatment preferably on the day of randomization, but no later than 3 days after randomization.
- A general ± 3 day window is permitted on assessments. A visit window ± 7 days is allowed on biochemistry assessments. Restrict the use of windows before Cycle 3 Day 1 when feasible.
- A general ± 3 days is allowed for goserelin administration.
- A visit window of + 3 days is allowed for EOT visit, ± 3 days for safety follow up visit.

- Radiological assessments and patient reported outcomes must be performed as outlined in Table 8-1. A visit window of ± 7 days is allowed.
- The whole body bone scan should be performed within 42 days or 6 weeks prior to randomization.
- Height, weight, vital signs, physical exam, ECOG performance status, hematology, biochemistry, should be performed within 14 days of randomization.
- **Note**: If the physical examination, ECOG performance status, and/or laboratory screening assessments were performed ≤ 7 days prior to the first dose of study treatments, then they do not need to be repeated on Cycle 1 Day 1.
- The ECG should be performed within 7 days prior to randomization.
- Patients' eligibility to participate in the study will be confirmed before randomization is performed and study drug is administered.
- Testing of FSH and/or estradiol (if necessary for determining pre-menopausal status for eligibility) and serum pregnancy test (β-Hcg) (unless the patient has had a hysterectomy) must occur within 28 days before starting study treatment.

All other screening assessments must be completed within 28 days before randomization (Cycle 1, Day 1). Every effort should be made to follow the schedule outlined in Table 8-1.

Table 8-1 Assessment Schedule

	Category	Reference to protocol section	Screening Phase		Treatment Phase								Survival Follow up
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3 to Cycle 12**	**In every 3rd Cycles (Cycle 15, 18, 21...)**	**End of study treatment (EOT) within 15 days from the last dose**	**Safety follow up EOT + 30 days**	**Survival Follow up (occurs every 16 (± 4) weeks after safety follow up visit)**
Treatment days			**-28 to -1**	**-14 to -1**	**1**	**15**	**1**	**15**	**1**	**1**			**N/A**
Screening													
Study Informed Consent, [redacted]	D	7	X										
IRT Screening (after ICF signature)	S	8.1	X										
Screening phase disposition	D	8.1	X										
Patient History													
Demography	D	8.2	X										
Inclusion / Exclusion criteria	D	5.1 and 5.2	X	X									
Relevant medical history / current medical conditions	D	8.2	X										
ER and PgR status	D	8.2	X										
HER2 status	D	8.2	X										
Diagnosis and extent of cancer	D	8.2	X										
Prior antineoplastic therapy	D	8.2	X										

	Category	Reference to protocol section	Screening Phase		Treatment Phase								Survival Follow up
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3 to Cycle 12**	**In every 3rd Cycles (Cycle 15, 18, 21...)**	**End of study treatment (EOT) within 15 days from the last dose**	**Safety follow up EOT + 30 days**	**Survival Follow up (occurs every 16 (± 4) weeks after safety follow up visit)**
Treatment days			**-28 to -1**	**-14 to -1**	**1**	**15**	**1**	**15**	**1**	**1**			**N/A**
Prior / concomitant medication	D	8.2	Continuous – up to 30 days after last dose										
Randomization													
Eligibility checklist (within IRT)	S	8.1.1			X								
IRT – randomization	D	8.1			X								
Physical examination													
Physical examination	S	8.4		X	X		X		X	X	X		
Performance status (ECOG)	D	8.4.1		X	X	X	X	X	X	X	X		
Height	D	8.4		X									
Weight	D	8.4		X	X		X		X	As clinically indicated	X		
Vital signs	D	8.4		X	X	X	X	X	X	X	X		
Laboratory assessments													
Hematology[2]	D	8.4.2.1		X	X	X	X	X	X	X	X		
Biochemistry (including fasting glucose)[2]	D	8.4.2.2		X	X	X	X	X	X	X	X		
FSH	S	8.4.2.3	X										
Plasma estradiol	S	8.4.2.3	X										

	Category	Reference to protocol section	Screening Phase		Treatment Phase								Survival Follow up
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3 to Cycle 12**	**In every 3rd Cycles (Cycle 15, 18, 21...)**	**End of study treatment (EOT) within 15 days from the last dose**	**Safety follow up EOT + 30 days**	**Survival Follow up (occurs every 16 (± 4) weeks after safety follow up visit)**
Treatment days			**-28 to -1**	**-14 to -1**	**1**	**15**	**1**	**15**	**1**	**1**			**N/A**
Coagulation [3]	D	8.4.2.4			Please refer to 8.4.2.4								
Tumor Assessment													
Tumor Assessment	D	8.3.2	X		Every 6 weeks for the first 12 weeks and at every 8 weeks for the next 32 weeks, and at every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, patient/guardian decision, and at EOT[1]. If PR/CR is reported, confirmation of response is required; confirmatory assessment should be performed ≥ 4 weeks after response is first documented.								
Whole body bone scan	D	8.3.2	X (within 42 days prior to randomization)		-								
Safety													
ECG (standard 12-lead)	D	8.4.3		X (Days -7 to Days -1)		X	X				X		
Serum Pregnancy Test	D	8.4.2.3	X										
Urine Pregnancy test	D	8.4.2.3			X		X		X	X	X		
Concomitant medications/procedures	D	6.2.1	X		Continuous						X	X	

	Category	Reference to protocol section	Screening Phase		Treatment Phase							Survival Follow up
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3 to Cycle 12**	**In every 3rd Cycles (Cycle 15, 18, 21...)**	**End of study treatment (EOT) within 15 days from the last dose**	**Safety follow up EOT + 30 days**	**Survival Follow up (occurs every 16 (± 4) weeks after safety follow up visit)**
Treatment days			**-28 to -1**	**-14 to -1**	**1**	**15**	**1**	**15**	**1**	**1**			**N/A**
Adverse events	D	10	X		Continuous						X	X	
End of Phase Disposition	D	8									X		
Patient Reported Outcome													
FACT-B	D	8.5	X		Every 6 weeks for the first 12 weeks and at every 8 weeks for the next 32 weeks, and at every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, patient/guardian decision, and at EOT							X	
[redacted]													
Treatment													
NSAI	D	6.1			Daily								
Goserelin	D	6.1			Day 1 of each cycle with an administration window of ± 3 days								
Ribociclib	D	6.1			Days 1-21 of each cycle								
Combination Chemotherapies	D	6.1			Please refer to “Treatment Information” Table 4-1.								
Discontinuation													
IRT – discontinuation	S	9.2									X		

	Category	Reference to protocol section	Screening Phase		Treatment Phase								Survival Follow up
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3 to Cycle 12**	**In every 3rd Cycles (Cycle 15, 18, 21...)**	**End of study treatment (EOT) within 15 days from the last dose**	**Safety follow up EOT + 30 days**	**Survival Follow up (occurs every 16 (± 4) weeks after safety follow up visit)**
Treatment days			**-28 to -1**	**-14 to -1**	**1**	**15**	**1**	**15**	**1**	**1**			**N/A**
Antineoplastic therapies since discontinuation of study treatment	D	3.1.2.1										X	
Survival follow-up	D	3.1.3											X

[1] The tumor evaluation at EOT is ONLY required for patients who discontinued the study treatments before the first scheduled post-baseline tumor assessment (week 6) OR for patients whose previous tumor assessment did not demonstrate PD and was done more than 21 days prior to end of treatment visit.

[2] Hematology and biochemical parameters need to be performed as indicated in the VES. Patients on combination chemotherapy may have additional hematology and biochemical assessments as per the local practice for such drug and are considered as standard of care.

[3] Coagulation parameters of INR or PT are to be performed at every visit only for the patients receiving oral coumarin-derivate anticoagulants such as warfarin and phenprocoumon along with capecitabine as one of the medication in the combination chemotherapy group.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again. Patients can be contacted more frequently than is required by the study protocol, with frequency selected according to circumstances and including the individual patient’s vulnerability to pandemic or epidemic. All modes of patient contact (virtual or writing) should have a proper source documentation for the trial.

8.1 Screening

Molecular pre-screening

Not applicable

Screening

After signing the study ICF, the screening assessments will be done within 1 to 28 days prior to randomization or within 1 to 14 days prior to randomization for selected assessments (see Table 8-1 for list of assessments to be performed); the ECG should be performed within 7 days prior to randomization.

Note: Any screening assessment that is done outside the screening window (Day -28 to Day -1 or Day -14 to Day -1 as applicable) must be repeated prior to randomization.

For laboratory evaluations used to determine eligibility, one repeated evaluation within the screening window is permitted for screening results out of the defined range before screen failing the patient. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility (multiple evaluations for serum electrolytes, blood counts and biochemistry parameters such as liver function and renal function are allowed). If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. No re-screening of patients is allowed in this study.

During the screening, if the patients' heart rate is above 100/min, beta-blocker will be allowed. Thereafter, if the patients' heart rate is under control, ECG shows no QTcF prolongation (>450 msec) and the patient is clinically and hemodynamically stable, they will be allowed to participate in the study. Assessments of patient reported outcomes should be collected prior to any clinical assessments, drug dosing or diagnostic testing.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to randomization (and 42 days for the whole body bone scan), including before signing the main study ICF can be considered as the baseline images for this study.

8.1.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Patients who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, visit date, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening phase (see SAE section (Section 10.1.3) for reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

Patients who are randomized and fail to start treatment, e.g. patients randomized in error, will be considered an early terminator and will be recorded in the IRT, along with reason for early termination. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Subject demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

The data that will be collected on patient characteristics at screening includes:

- Demography (Age, sex, race, ethnicity).
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade. No additional medical assessments will be performed to confirm the current medical condition.
- ER, PgR, and HER2 status.
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.
- Patient-reported outcome questionnaires (FACT B) (See Section 8.5).

Furthermore the following assessments will be performed:

- Vital signs
- Height, weight
- Physical examination
- Performance status (ECOG)
- Laboratory evaluations (hematology, chemistry)
- ECG
- Radiological assessments (e.g. CT Scan)

8.3 Efficacy

8.3.1 Efficacy Assessment

Tumor assessments will be performed:

- at screening (Day -28 to -1) and

- at every 6 weeks after randomization/first dose for the first 12 weeks and
- at every 8 weeks for the next 32 weeks and
- at every 12 weeks thereafter until disease progression (radiologically documented according to RECIST 1.1 criteria) or death, withdrawal of consent, loss to follow-up, patient/guardian decision
- at End of Treatment (EOT): Only required for patients who discontinued the study treatments before the first scheduled post-baseline tumor assessment (week 6) OR patients whose previous tumor assessment did not demonstrate PD and was done more than 21 days prior to end of treatment visit

At the Screening (Day -28 to Day -1), if any site has any record of CT scan that is performed within 28 days prior to randomization for a particular patient, the CT scan need not be re-performed for that patient and that image can be considered as the baseline images for this study.

Following treatment discontinuation, all patients (except if consent is withdrawn or patient is lost to follow-up) will be followed for survival at least every 16 (± 4 weeks after the safety follow-up visit), until at least either 80% deaths have been documented or at least 46 months elapsed since FPFV, whichever occurs first.

8.3.2 Imaging tumor assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.2 (Appendix 2) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 8-2.

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

Imaging assessments will be performed at screening within 28 days prior to randomization and subsequently at every 6 weeks for the first 12 weeks and at every 8 weeks for the next 32 weeks and at every 12 weeks thereafter (± 7 days), until disease progression (radiologically documented according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision. Imaging assessment performed during the screening phase (between Day -28 to Day -1) should be considered as the baseline image. The details of assessments is provided in Table 8-1. The interval between imaging assessment should be respected regardless of whether study treatment is temporarily withheld. Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a patient, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment. After baseline, all assessments should be performed within ± 7 days of the scheduled day of assessment. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up. Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent

imaging assessments should be performed in accordance with the original imaging schedule. To the extent possible, each lesion should be assessed using the same imaging method throughout the study.

All patients will undergo CT or MRI of the chest, abdomen and pelvis at baseline and subsequent scheduled visits per Table 8-1. The preferred imaging methodology is CT with intravenous (i.v.) contrast. However, if at baseline, a patient is known to have a contraindication to CT i.v. contrast media or develops a contraindication during the trial, a non-contrast CT of chest (MRI is not recommended due to respiratory artifacts) plus contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

A whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, FDG-PET or sodium fluoride positron emission tomography (NaF PET)) should be acquired at baseline for all patients if not collected previously within 42 days (6 weeks) prior to randomization. Skeletal lesions identified on the whole body bone scan at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI or X-ray. Whole body bone scans need not be repeated after baseline unless clinically indicated.

Color photography, including a metric ruler to estimate the size of the lesion, must be acquired for all **skin lesions** present at screening. These should be followed throughout the study according to the schedule outlined in Table 8-1.

Other metastatic disease sites will be followed by CT or MRI, as clinically indicated.

Chest X-ray or ultrasound should not be used to assess tumor lesions.

Combined Positron Emission Tomography (PET)/CT may be used only if the CT component is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 2). If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Any lesions in previously irradiated areas should not be considered measurable unless they have experienced progression since the radiotherapy. Any pre-existing radiographic findings which may mimic metastatic disease and any prior radiotherapy should be recorded in the eCRF.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to randomization (and 42 days for the whole body bone scan), including before signing the main study ICF can be considered as the baseline images for this study.

If an off-schedule imaging assessment is performed to confirm response or if progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Physical exam tumor assessments, photography, pathology/histology and cytology results, as well as information regarding prior interventions, pre-existing radiographic findings that mimic metastatic disease at baseline/screening and on-study interventions should be captured in the appropriate eCRFs and may be -for additional review if appropriate.

A tumor evaluation at EOT is required:

- for patients who discontinue treatment before first scheduled post-baseline tumor assessment (week 6) or
- for patients whose previous tumor assessment did not demonstrate PD and was done more than 21 days prior to end of treatment visit.

Efficacy assessments should continue as per the scheduled visit provided in Table 8-1.

Table 8-2 Imaging Assessment Collection Plan

Procedure	Screening: day −28 to day -1	Treatment phase*	End of treatment*
CT or MRI (Chest, Abdomen, Pelvis)	Mandated	Every 6 weeks for the first 12 weeks and at every 8 weeks for the next 32 weeks, and at every 12 weeks thereafter (± 7 days) until disease progression (radiologically documented according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision	Mandated
Brain CT or MRI	Only if suspected brain metastases	Only if suspected brain metastases	
Whole body bone scan**	Mandated, within 42 days (6 weeks) prior to randomization.	As clinically indicated	As clinically indicated
Bone X-ray, CT or MRI	Only if skeletal abnormalities identified by whole body bone scan (or skeletal survey) at screening, which are not visible in the chest, abdomen, pelvis CT/MRI.	If bone lesion at screening, every 6 weeks for the first 12 weeks and at every 8 weeks for the next 32 weeks, and at every 12 weeks thereafter (± 7 days), until disease progression (radiologically documented according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision	Mandated only if bone lesion at screening

Procedure	Screening: day −28 to day -1	Treatment phase*	End of treatment*
Skin color Photography	Only if skin lesions at screening	If skin lesions at screening, every 6 weeks for the first 12 weeks and at every 8 weeks for the next 32 weeks, and at every 12 weeks thereafter (± 7 days), until disease progression (according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision	Mandated if skin lesions at screening
CT or MRI of any disease outside of chest, abdomen and pelvis (e.g., neck)	Only if suspected lesion at screening	If lesion identified at screening, every 6 weeks for the first 12 weeks and at every 8 weeks for the next 32 weeks, and at every 12 weeks thereafter (± 7 days) until disease progression (radiologically documented according to RECIST 1.1 criteria), death, withdrawal of consent, loss to follow-up, or patient/guardian decision	Mandated if lesion at screening

*Tumor evaluation at EOT is required for patients who discontinue study treatment before the first scheduled post-baseline tumor assessment (week 6) and for patients whose previous tumor assessment did not demonstrate PD and was done more than 21 days prior to end of treatment visit.

** Whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, sodium fluoride positron emission tomography (NaF PET) or fluorodeoxyglucose (FDG) PET.

Note: All scans will be read locally

8.3.3 Appropriateness of efficacy assessments

Tumor response measurements are standard and will be assessed according to the Novartis guideline version 3.2 (Appendix 2) based on RECIST Version 1.1 (Eisenhauer et al 2009).

8.4 Safety

Safety will be monitored by assessing physical examinations, ECOG performance status, height and weight, vital signs, ECG, patient reported outcomes, laboratory assessments including hematology, biochemistry, pregnancy, and coagulation parameters such as INR or PT (to be performed only for the patients receiving capecitabine as one of the medication in the combination chemotherapy group along with oral coumarin derivate anticoagulants such as warfarin and phenprocoumon) as well as collecting of the adverse events at every visit. All the safety assessment will be performed according to the visit schedule as outlined in Table 8-1.

For details on AE collection and reporting, refer to Section 10.1. Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF. The list of the physical assessments planned for this study are provided in Table 8-3.

Table 8-3 Physical Assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological review. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. - Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital sign	Vital signs include blood pressure and pulse measurements and body temperature. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 – 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks for ribociclib arm and every 3 weeks for combination chemotherapy arm or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Physical assessment/s can be performed by another qualified breast cancer physician or medical oncologist outside study site. The process for assuring oversight of the same, including communication to confirm patient safety should be in place. All relevant source documents certified by other breast cancer treating physician/s or medical oncologist/s should be retrieved and maintained in patients' medical record or charts at study site. Decisions related to patients' discontinuation for treatment will be based on investigators' full review of results of laboratory and safety assessment, patient's physical assessment of health status, clinical judgment and/or patient's own decision.

8.4.1 Performance status

The performance status will be assessed according to the ECOG performance status scale (Oken et al 1982) following the schedule given in Table 8-4.

Table 8-4 ECOG performance status

Grade	ECOG status
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

8.4.2 Laboratory evaluations

Clinical laboratory analyses (hematology and chemistry) are performed by the local laboratory. Visit windows of ± 3 days are allowed for all visits except at Cycle 1 Day 1; a visit window ± 7 days is allowed on biochemistry assessments.

Novartis must be provided with a copy of the laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

At any time during the study, abnormal laboratory parameters which are clinically relevant (At decided by the investigator) and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the adverse event eCRF page. Laboratory data will be summarized using the CTCAE version 4.03. Additional analyses are left to the discretion of the investigator.

Table 8-5 Laboratory Assessments

Test Category	Test Name
Hematology	White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), hemoglobin (Hgb) and platelet count.
Biochemistry with fasting glucose	Potassium, uric acid, urea or BUN, creatinine, fasting glucose, calcium, corrected calcium, magnesium, and albumin. AST (SGOT), ALT (SGPT), total bilirubin, direct bilirubin, GGT and alkaline phosphatase, Amylase, lipase and LDH.
Coagulation	PT International normalized ratio [INR] or protrombin time. Please refer to Section 8.4.2.4.
Pregnancy Test	FSH, estradiol (for premenopausal patients only), serum pregnancy, and urine pregnancy test (dipstick)

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, Laboratory panels (e.g. Biochemistry and Hematology) can be performed at a certified local laboratory outside study site by supplying the patient with a lab request form, if feasible. All local lab reports (along with reference ranges) done outside of study site should be collected and filed in the patient medical records or charts at the study site.

Principal investigator should exercise discretion to consider other safety assessments that need to be conducted outside of the study site to ensure the patient's safety.

8.4.2.1 Hematology

Hematology tests are to be performed according to the visit schedules outlined in Table 8-1. Patients on combination chemotherapy may have additional hematology assessments as per the local practice for such drug and are considered as standard of care.

For details of the Hematology panel, refer to Table 8-5.

Note: If the laboratory screening assessments were performed ≤ 7 days prior to the first dose of study treatments (for both ribociclib and combination chemotherapies), then they do not need to be repeated on Cycle 1 Day 1.

Hematology should be assessed on the scheduled day, even if study drug is being withheld.

8.4.2.2 Biochemistry

Biochemistry tests are to be performed according to the visit schedules outlined in Table 8-1. Patients on combination chemotherapy may have additional biochemical assessments as per the local practice for such drug and are considered as standard of care.

For details of the biochemistry panel refer to Table 8-5.

Note: If the laboratory screening assessments were performed ≤ 7 days prior to the first dose of study treatments (for both ribociclib and combination chemotherapies), then they do not need to be repeated on Cycle 1 Day 1.

Biochemistry should be assessed on the scheduled day, even if study drug is being withheld.

8.4.2.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. FSH, estradiol, and serum or urine pregnancy tests (patients who have undergone a hysterectomy do not need pregnancy tests performed) are to be performed according to the Visit Schedules outlined in Table 8-1. If the laboratory screening assessments were performed ≤ 7 days prior to the first dose of study treatments (for both ribociclib and combination chemotherapies), then urine pregnancy test need not be repeated on Cycle 1 Day 1. At screening, a serum pregnancy test should be performed regardless of the age of the patients, while at baseline, during the study, and at the end of study, urinary pregnancy tests (dipstick) are sufficient. A positive pregnancy test requires immediate interruption of study treatment until the assessment is confirmed by the Principal Investigator. If positive, the patient must be discontinued from the study and perform EOT visit.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, patient can perform the urine pregnancy test at home and report the result to the site. Patient should be instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (following Country specific measures).

8.4.2.4 Coagulation

At every visit, INR or PT are to be performed only for the patients receiving capecitabine (as one of the medication in the combination chemotherapy group) along with oral coumarin-derivate anticoagulants such as warfarin and phenprocoumon.

Oral coumarin-derivate anticoagulants such as warfarin and phenprocoumon should be avoided in patients receiving capecitabine as study treatment. If patient needs to take coumarin-derivate anticoagulants anticoagulant response (INR or prothrombin time) should be monitored frequently in order to adjust the anticoagulant dose based on capecitabine prescribing information. Altered coagulation parameters and / or bleeding, including deaths have been reported during concomitant use.

8.4.3 Electrocardiogram (ECG)

Standard 12 lead ECG must be recorded after 10 minutes rest in the supine position, prior to each time point indicated in Table 8-6. The QTcF should be used for clinical decisions. Single reading of ECG is required at schedule days, including at the screening phase. Eligibility will be based on the ECGs conducted at screening. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

Table 8-6 Timing of study procedures

Cycle	Patients	Day	Time	ECG Type
Screening	All	-7 to -1	Anytime	12 Lead
1	All	Day 15	Pre-dose[1]	12 Lead

2	All	Day 1	Pre-dose[1]	12 Lead
EOT			Anytime	12 Lead
Unscheduled ECG			Anytime	12 Lead

[1]The exact date of dosing must be recorded on the appropriate eCRF
*Single reading of ECG is required for all cycles

If any of the readings include an abnormal ECG or an average QTcF value of ≥ 481 is obtained at any time after randomization, study treatment must be interrupted, repeat ECG and follow management guidelines detailed in Section 6.5.1 (for ribociclib treatment arm) and in Section 6.5.3 (for combination chemotherapies arm).

An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected. Local cardiologist ECG assessment may be performed at any time during the study at the discretion of the investigator.

Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening should be reported on the Medical History CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, ECGs (as required) can be performed by a qualified healthcare professional outside study site by providing the patient with a requisition form, if feasible. ECG tracings/reports done outside of study site should be collected and filed in the patient medical records or charts at the study site.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

8.5 Patient reported outcomes (PRO)

FACT-Breast (FACT-B) is a breast cancer-specific module to explore patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms and treatment-related side effects. The FACT-B (Brady et al 1997) is a recognized, reliable and valid instrument frequently used in clinical trials of patients with advanced or metastatic breast cancer. The English FACT-B version 4 are divided into five subscales, namely physical (PWB), social/family (SWB), emotional (EWB), functional well-beings (FWB), and the additional concerns for breast cancer (BCS) (Cheung et al 2014). The Scores will be added to create subscale and overall scores.

The FACT-B quality of life questionnaire (see Appendix 3) will be administered at study site before any study drug administrations at the visits indicated in Table 8-1 utilizing paper questionnaire for data collection. After that, all the answers provided by the patient will be transcripted into the eCRF by the investigator or delegated study personal. Collection of the FACT-B PRO has up to -7 day window unless otherwise indicated.

All questionnaires should be administered in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient's perspective. This is to avoid potentially biasing patients or their responses to study questionnaires. Patients should be given sufficient space and time to complete the study questionnaire and the administered questionnaire should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to the questionnaire for all patients, including from those who discontinue prior to the study evaluation completion visit, however, if patients refuse to complete the questionnaire, this should be documented in study source records. A patient's refusal to complete the study questionnaire is not considered a protocol deviation.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, must be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in Section 10 of this protocol. Investigators should not encourage the patients to change responses reported in questionnaires.

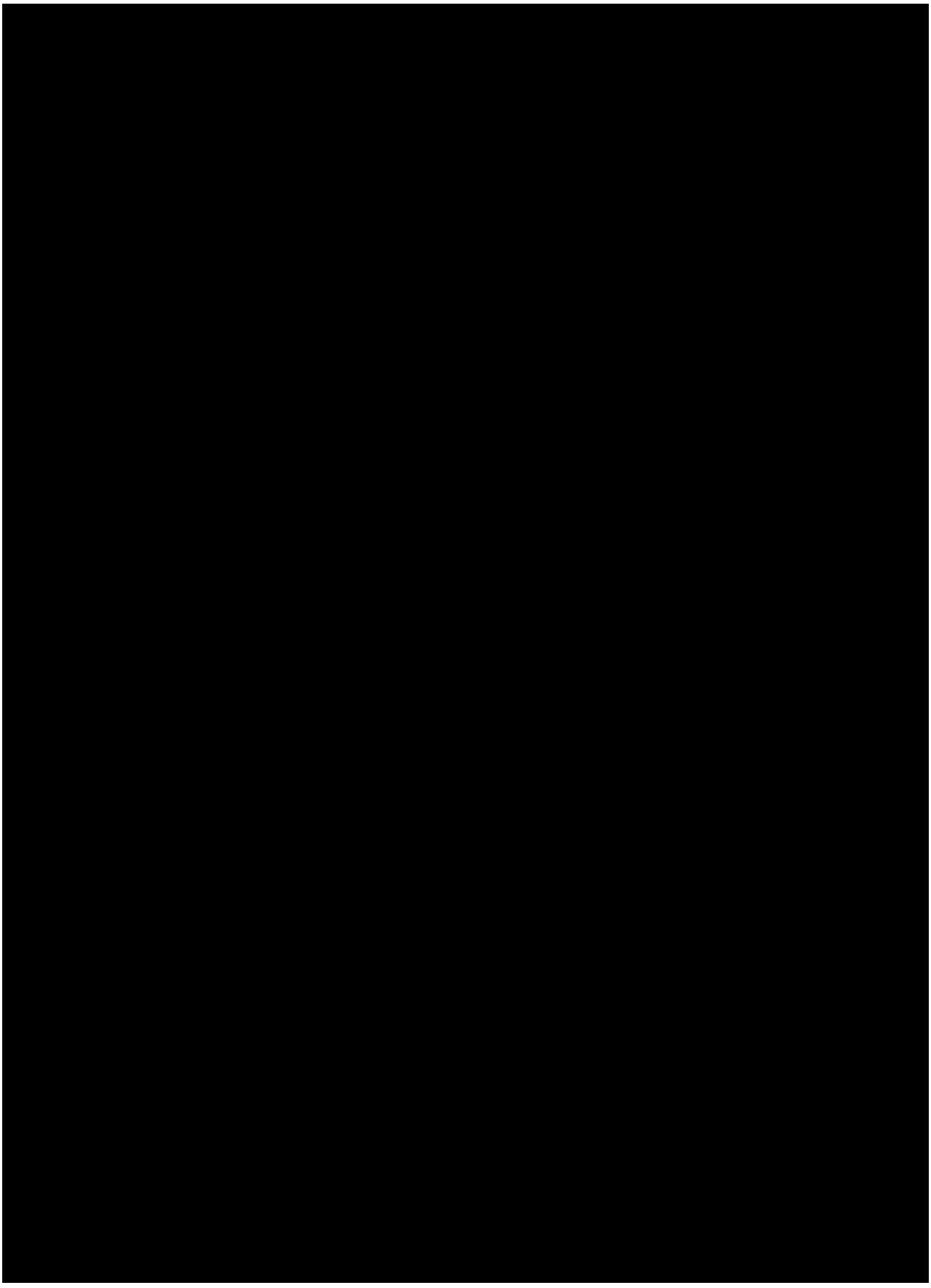
Table 8-7 Patient reported outcomes collection plan

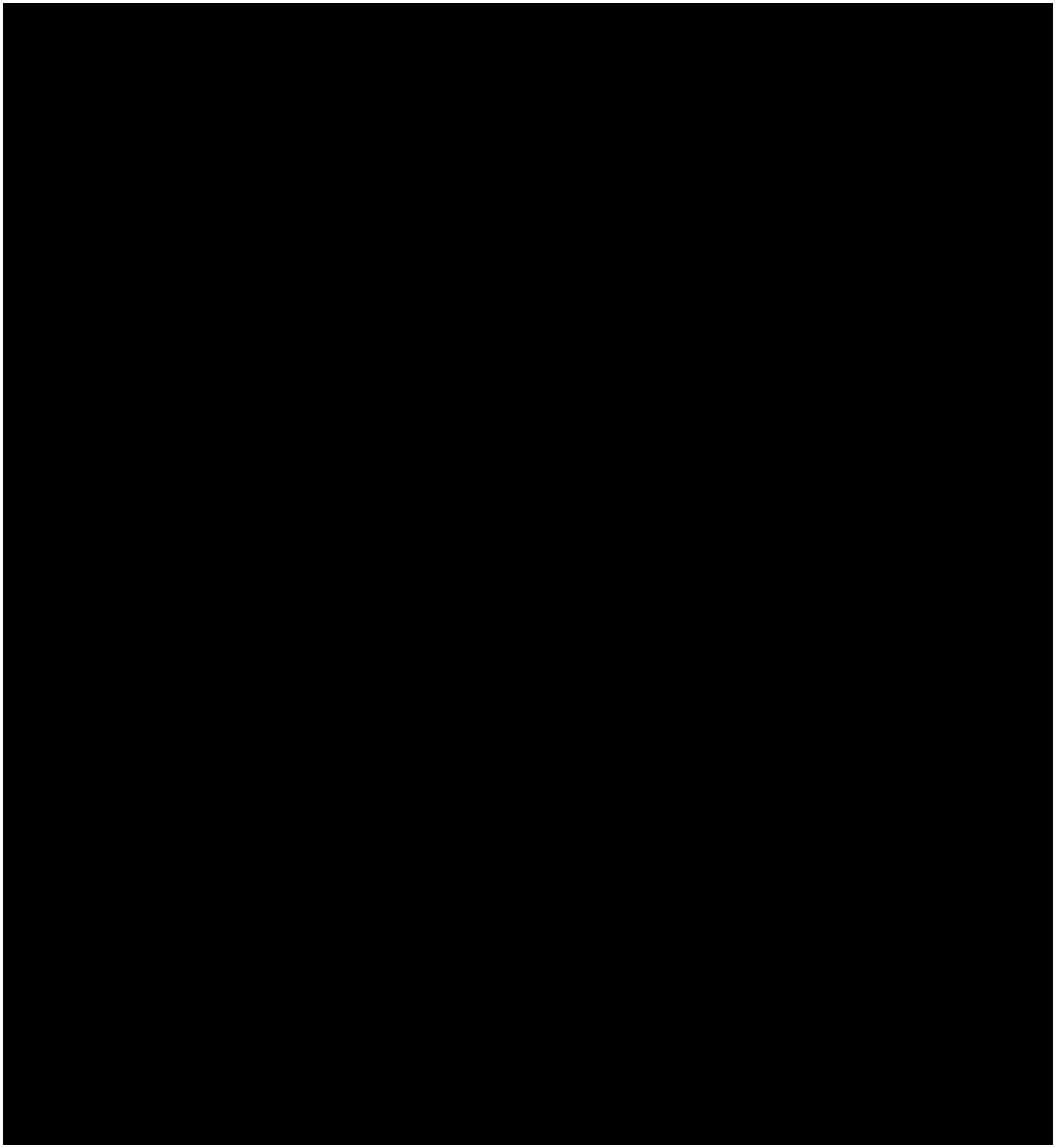
Patient Questionnaire	Cycle	Day	Time
FACT-B	Screening	-28 to Day -1	Prior to any clinical assessments, drug dosing or diagnostic testing.
	Subsequent cycles	Every 6 weeks for the first 12 weeks and at every 8 weeks for the next 32 weeks, and at every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, patient/guardian decision.	
	End of treatment	Day of EOT visit	
	Safety follow-up	Day of Safety follow-up visit	

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, FACT-B data may be collected remotely (e.g. telephone interviews) if allowed by local regulations and site personnel has the knowledge and expertise to perform it.

[redacted]

[redacted]





[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Both patient and investigator may voluntarily discontinue from the study treatment for any reason at any time.

The investigator must discontinue study treatment for a given patient if, he/she believes that continuation would negatively impact the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Adverse Event (including, but not limited to QTcF ≥ 501 msec, confirmed at repeated ECG measurements and recurrent after dose adjustment was performed; documented episode of ventricular tachycardia, or ventricular fibrillation)
- Lost to follow-up
- Physician decision
- Progressive Disease
- Any other protocol deviation that results in a significant risk to the patient's safety
- Study terminated by sponsor
- Technical problems
- Non-compliant with study treatment
- No longer requires treatment

Patients must be withdrawn from the study treatment if any of the following occur:

- Pregnancy
- Death
- Patient/Guardian decision

In addition to the general withdrawal criteria, the following study specific criteria will also require study treatment discontinuation:

- Adjustments to study treatment due to toxicity that result in discontinuation. Please refer to Section 6.5.1 (for ribociclib treatment arm) and Section 6.5.3 (for combination chemotherapies arm)
- Use of prohibited medication. Please refer to Section 6.2.2.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule. Patients who discontinue study treatment should undergo an EOT visit followed by a 30 day safety follow-up visit.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

For the detail of information to be collected, refer to Table 8-1. The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate Disposition CRF.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 9.2 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 or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion

An end of treatment (EOT) visit will be performed when the patient permanently discontinues all study treatment and the end of treatment procedures are completed.

End of study will be either on completion of at least 46 months from FPFV or when 80% of OS events have been reached, whichever occurs first. All randomized and/or treated patients should have a safety follow-up visit conducted 30 days after EOT visit. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the patient should be recorded in the source documentation.

The primary analysis will occur when approximately the required 110 of PFS events is reached. After the primary analysis of PFS, the study will remain open provided the PFS demonstrates treatment benefit. Patients still being followed on the study after the primary analysis time point will continue as per the schedule of assessments. The study will end once the final OS analysis is performed approximately after 46 months from FPFV or when the 80% patient dies (whichever comes first). If the primary analysis of PFS does not demonstrate treatment benefit, the follow-up for OS will end.

On EOT, patients should be scheduled for an EOT visit within 15 days following the date study treatment is permanently discontinued, at which time all of the assessments listed for the EOT

visit will be performed. For details of assessments, refer to Table 8-1. If the decision to discontinue the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. An End of treatment disposition eCRF page should be completed, giving the date and reason for stopping the study treatment.

If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the EOT eCRF page. The EOT visit is not considered the end of the study.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations up to 45 days (within 15 days after the last dose and 30 days after the EOT visit) following the last dose of study treatment.

The Investigator must contact the IRT to register the patient's discontinuation.

Patients continuing to derive benefit from study treatment at the end of the study in the opinion of the investigator may be transferred to a PTA following the local country Health Authority regulation(s) and patient's consent, if ribociclib is either not commercially available or not reimbursed to the patients in the country by the time the study is completed. If at the end of the study, patients continuing to derive benefit from comparator treatment in the opinion of the investigator will transition onto the commercial available product(s), which should be accessible via their healthcare provider in the respective countries. If the comparator treatment is commercially available but not reimbursed, an alternative option may be discussed between the investigator and Novartis team.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.3):

1. Adverse events will be assessed and graded 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 but is collected as seriousness criteria; rather, information about deaths will be collected though a Death form.
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.3 for definition of SAE) and which seriousness criteria have been met
5. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown).

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn
- its outcome i.e., its recovery status or whether it was fatal

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. Continuing at the end of the study), and assessment must be made at each

visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease. Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a serious adverse event unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

If any information for the patient harboring infection related to pandemic or epidemic (e.g. COVID-19) becomes known to investigator or his/her team through patient/care-giver, it should be informed to Novartis team. If a patient is confirmed positive for pandemic and/or epidemic infection, it should be recorded as an adverse event. Any events associated with it should be recorded/reported either as non-serious AE or SAE based on the seriousness criteria of the event.

10.1.2 Adverse events of special interest

Adverse events of special interest are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. Adverse events of special interest are discussed in detail in the IB.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Screen failures:

As patient is considered screen failure who is screened but is not treated or randomized SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

Randomized or treated patients:

SAEs collected between time patient signs ICF until 30 days after the patient has discontinued or stopped study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to one year after the baby was due to be born to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe.

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- note that hospitalizations for the following reasons should not be reported as serious adverse events :
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an

emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.6 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

Not applicable

10.2.1 Data Monitoring Committee

Not applicable

10.2.2 Steering Committee

The steering committee will be established comprising investigators, Novartis personnel participating in the trial and one patient, who is not participating in this trial.

The steering committee will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The steering committee will review protocol amendments as appropriate. Together with the clinical trial team, the steering committee will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about study treatment (ribociclib only) dispensed to the patient will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis to be accessed by programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis- development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis /delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12 Data analysis and statistical methods

It is planned that the data from all centers participating in the trial will be combined, so that an adequate number of patients are available for analysis. Novartis and/or a designated CRO will perform all analyses.

Any data analysis carried out independently by any investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

12.1.1 Full Analysis Set

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

12.1.2 Safety Set

The Safety Set (SS) includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

12.1.3 Per-protocol Set

The Per-Protocol Set (PPS) is a subset of patients of the FAS who are compliant with requirements of the protocol. All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the data handling plan and analysis plan. Sensitivity analyses of the primary endpoint may be performed using data from the PPS if the FAS and PPS differ and if the primary analysis is significant.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25^{th} and 75^{th} percentiles (if appropriate), minimum, and maximum will be presented.

The actual dose and duration of NSAI, goserelin, ribociclib and combination chemotherapy, as well as dose intensity (computed as the ratio of the dose intensity to planned dose received/ planned duration), will be listed and summarized using descriptive statistics. The total daily doses of NSAI, goserelin, ribociclib and combination chemotherapy for each patient will be summarized using descriptive statistics.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, for each treatment group.

Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions. The duration of exposure will also be presented for the study treatment by arm.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group and all dosing data will be listed.

12.4 Analysis of the primary endpoint

PFS will be summarized using Kaplan-Meier estimates. Median PFS with 95% confidence intervals will be provided by treatment group. Stratified Cox regression will be used to estimate the hazard ratio (HR) of PFS, along with 95% confidence intervals.

12.4.1 Definition of primary endpoint

The primary endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via local review according to RECIST 1.1 (see Appendix 2 for further details).

12.4.2 Statistical model, hypothesis, and method of analysis

Assuming proportional hazards for PFS, the following statistical hypotheses will be tested to address the primary efficacy objective:

$$\mathrm{H}_{01}: \theta_1 \geq 1 \; vs. \; \mathrm{H}_{A1}: \theta_1 < 1$$

where θ_1 is the PFS hazard ratio (ribociclib + NSAI + goserelin arm versus combination chemotherapy arm). The primary efficacy analysis to test these hypotheses and compare the two treatment groups will consist of a stratified log-rank test at an overall one-sided 10% level of significance.

The primary efficacy variable, PFS, will be analyzed once 110 PFS events are observed. The PFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model.

12.4.3 Handling of missing values/censoring/discontinuations

In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date.

If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment before the PFS event. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used (see RECIST 1.1 in Appendix 2). PFS will be censored at the date of the last adequate tumor assessment before the start of new anticancer therapy if no PFS event is observed prior to and after the start of new antineoplastic therapy.

12.4.4 Sensitivity and Supportive analyses

As a sensitivity analysis, the distribution of PFS will be compared between the treatment groups using an un-stratified log-rank test and the hazard ratio along with the associated 95% confidence interval resulting from an un-stratified Cox model will be presented.

Sensitivity analyses of the primary endpoint may be performed using data from the PPS if the FAS and PPS differ and if the primary analysis is significant. Other sensitivity analyses may be performed such as (1) including PFS events even if the events are recorded after two or more missed assessments, (2) backdating events occurring after missing tumor assessments. Patterns of censored data will be examined by the treatment groups using descriptive statistics (the numbers of censored patients and reasons for censoring) (3) including PFS events documented after initiation of new anti-neoplastic therapy and (4) using the primary analysis source on the FAS and considering treatment discontinuation due to 'Disease Progression' without documented progression as event. Sensitivity analyses considering COVID-19 impact will be included in the SAP.

12.5 Analysis of secondary endpoints

The secondary objectives in this study are to compare the two treatment groups with respect to OS, to evaluate the ORR, CBR, TTR, TTF, 3-month TFR, safety and PROs for health related QoL.

12.5.1 Efficacy endpoints

Overall survival (OS) is defined as the time from date of randomization to date of death due to any cause. If a patient is not known to have died, then OS will be censored at the latest date the patient was known to be alive.

OS will be analyzed in the FAS population according to the randomized treatment group assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

Overall response rate (ORR) is defined as the proportion of patients with best overall response (BOR) of CR or PR, as per local review and according to RECIST 1.1 (see Appendix 2 for details).

ORR will be calculated based on the FAS population. ORR and its 95% confidence interval will be presented by treatment group. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor, will be used to compare ORR between the two treatment groups, at the one-sided 5% level of significance.

Clinical benefit rate (CBR) is defined as the proportion of patients with a BOR of CR, or PR or an overall response of SD, lasting for a duration of at least 24 weeks. CR, PR and SD are defined as per local review according to RECIST 1.1 (see Appendix 2 for details).

CBR will be calculated based on the FAS and according to the intent-to-treat (ITT) principle. CBR and its 95% confidence interval will be presented by treatment group. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor, will be

used to compare CBR between the two treatment groups, at the one-sided 5% level of significance.

Time to Response (TTR) is defined as the time from the date of randomization to the first documented response of either CR or PR, which must be subsequently confirmed (although date of initial response is used, not date of confirmation). CR and PR are based on tumor response data as per local review and according to RECIST 1.1 (see Appendix 2 for details).

All patients in the FAS will be included in TTR calculations. Patients without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e., LPLV-FPFV) for patients with a PFS event (i.e., disease progression or death due to any cause), or at the date of the last adequate tumor assessment for patients without a PFS event. TTR will be listed and summarized by treatment group. Distribution of time to response will be estimated using Kaplan-Meier method if sufficient number of responses are recorded.

Time to treatment failure (TTF) is defined as the time from the date of randomization to the earliest of date of progression (as per local review and according to RECIST 1.1), date of death due to any cause, change to other anti-cancer therapy, or date of discontinuation due to reasons other than protocol violation or administrative problems. All patients in the FAS will be included in TTF calculations. TTF will be listed and summarized by treatment group.

Treatment failure rate (TFR) is defined as the proportion of patients who discontinued the study treatment due to death of any cause, progressive disease (as per local review and according to RECIST 1.1), change to other anti-cancer therapy, or change of treatment. All patients in the FAS will be included in 3-month TFR. 3-month TFR will be summarized by treatment group.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

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, which started or worsened during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

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

- pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- post-treatment period: starting at Day 31 after last dose of study medication.

Adverse events

All information obtained on adverse events will be displayed by treatment group and patient.

The number (and proportion) of patients with AEs of special interest/related to identified and potential risks will be summarized by treatment.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Investigator's Brochure].

AESI include: Neutropenia including febrile neutropenia, QT prolongation, and hepatobiliary AEs.

A patient with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of AE, relation to study treatment.

Serious AEs, non-serious AEs and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious AEs (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each patient during the study. ECG data will be read and interpreted (locally).

Categorical Analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these patients will be produced (by treatment group).

All ECG data will be listed by treatment group, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version available at the time of analysis.

The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

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

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

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE available at the time of analysis grades if applicable and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE available at the time of analysis.

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades available at the time of analysis to compare baseline to the worst on-treatment value.
- For laboratory tests where grades are not defined by CTCAE available at the time of analysis
- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

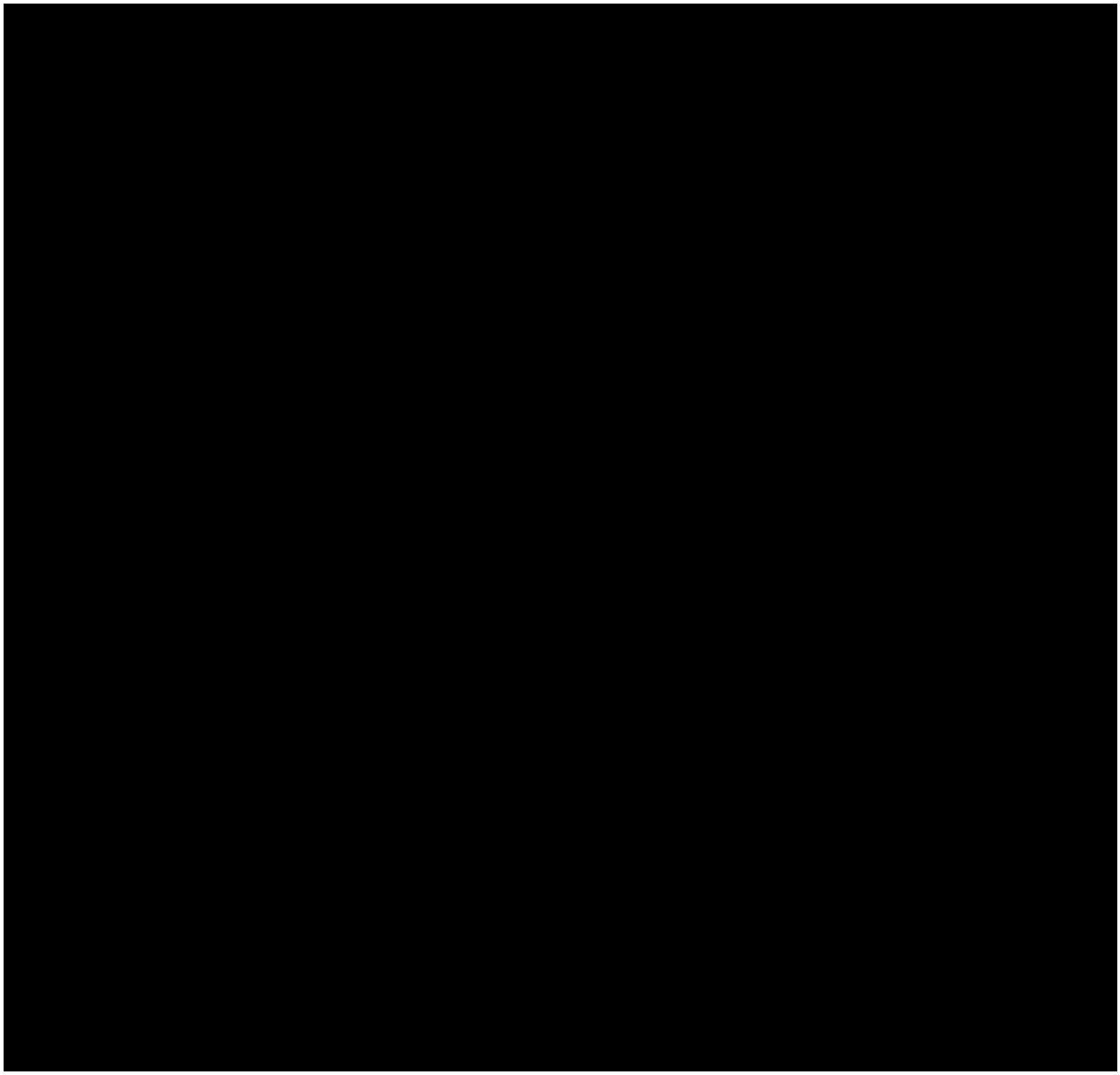
12.5.3 Patient reported outcomes

FACT-B questionnaire will be used to collect patient reported outcome data in this trial. Scores will be added to create subscale and overall scores.

The FAS will be used for analyzing PRO data. Descriptive statistics will be used to summarize the subscale and overall scores at each scheduled assessment time point. Additionally, change from baseline at the time of each assessment will 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. Time to deterioration in the PRO scales will be performed and compared between the two treatment arms.

[redacted]

[redacted]



12.7 Interim analyses

No interim analysis is planned.

12.8 Sample size calculation

The sample size calculation is based on the primary analysis of PFS. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

Based on available data, the median PFS in the control arm is expected to be approximately 12 months. It is expected that treatment with ribociclib arm will result in a 33% reduction in the hazard rate for PFS, i.e., an expected hazard ratio of 0.667 (which corresponds to an increase in median PFS to 18 months under the exponential model assumption).

Then in order to ensure 80% power to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: PFS hazard ratio = 0.667, it is calculated that a total of 110 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 10% level of significance, patients randomized to the two treatment arms in a 1:1 ratio. Considering that enrolment will continue for about 30 months, 3 patients for 0-6 months, 10 patients for 7 -17 months and 6 patients thereafter, a total of 200 patients will be needed to observe the targeted 110 PFS events at about 4 months after the randomization date of the last patient. Assuming 10% drop-out, a total of 222 patients will be needed. The sample size of 222 patients will be randomly assigned to each treatment arm in a 1:1 ratio (111 patients in the experimental arm, 111 patients in the control arm). These calculations were made using the software package East 6.4.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or

transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (i.e., LPLV) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1 – Concomitant medication

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or ribociclib.

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on Novartis PK Sciences Memorandum, Drug-Drug Interaction and Co-Medication Considerations for Novartis Clinical Trials (, release date: Jan 2018), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http://www.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (www.qtdrugs.org/). Please contact the medical monitor with any questions.

The following medications (Table 16-1) are prohibited during combined ribociclib, NSAI, and goserelin treatment in this study.

Table 16-1 List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir,ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Apalutamide, carbamazepine[3], enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin[3], rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[2,3]
CYP3A4/5 substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lomitapide[5], lovastatin, nicardipine, nisoldipine, pimozide, quinidine, simvastatin, sirolimus, tacrolimus

Category	Drug Name
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, gatifloxacin, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, levomethadyl, mesoridazine methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terlipressin, terodiline, terfenadine, thioridazine, vandetanib
Herbal preparations/ medications or dietary supplements	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 include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, and ginseng. Patients should stop using these herbal medications or dietary supplements 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, hormonal therapy, including but not limited to all SERMS [including raloxifene], biologic or radiation therapy [except for palliative radiotherapy as outlined in the protocol], and surgery) other than the study treatments must not be given while the patient is on the study medication. If such agents are required, then the patient must discontinue the 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) or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.

[2] Herbal product

[3] P-gp inducer

[4] The list provided is as of December 2019.Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

[5] Drug has warning for risk of hepatotoxicity. 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.

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

The following medications (Table 16-2) should be used with caution during combined ribociclib, NSAI, and goserelin treatment in this study.

Table 16-2 List of medications to be used with caution during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Aprepitant, Amprenavir, asafoetida resin (Ferula asafoetida), cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein, lopinavir[5], modafinil, nafcillin, telotristat.
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, apixaban, aprepitant, atorvastatin, avanafil, bosutinib, brotizolam, budesonide, buspirone, cannabinoids[6], cannabidiol[6],, cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, , lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, perospirone, quetiapine, ridaforolimus, rivaroxaban, sildenafil, simeprevir, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin
BSEP inhibitors	Alectinib, atorvastatin, , bromocriptine, candesartan, clobetasol, clofaziminie, , dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone, pioglitazone, reserpine, rifamycin, simeprevir, telmisartan, timcodar, troglitazone, velpatasvir
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, atazanavir, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib, clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine (retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, loperamide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, nilotinib, norfloxacin, nusinersen, nortriptyline, ofloxacin, olanzapine, osimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, quetiapine, ranolazine, rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, telavancin, tetrabenazine, tipiracil/trifluridine, tizanidine, tolterodine, toremifene, trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT1/2 substrates[4]	Amantadine, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxaliplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium, and zidovudine

Category	Drug Name
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, ethinyl estradiol, irinotecan, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax.

[1] Sensitive substrates include drugs whose plasma AUC values have been shown to increase 5-fold or higher when co- administered with a potent inhibitor.

[2] The list provided is as of January 2018. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

[3] MATE1 and MATE2 share considerable substrate specificity.

[4] OCT1 and OCT2 share considerable substrate specificity.

[5] Lopinavir and atazanavir is prohibited when combined with ritonavir (see Table 14-1)

[6] Based data that, exposure of cannabidiol (CBD), tetrahydrocannabinol (THC), 11-hydroxy THC, increased by ~2-3 folds when co-administered with ketoconazole (CYP3A4 inhibitor); Stott et al, Springerplus. 2013; 2: 236

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

16.2 Appendix 2: Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

16.2.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 16.2.2 and the definition of best response in Section 16.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.3.2 is summarizing the “time to event” variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.4 of this guideline describes data handling and programming rules. This section is to be referred to in the Reporting and Analysis Plan (RAP) to provide further details needed for programming.

16.2.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

16.2.3 Definitions

16.2.3.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - 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 patients without measurable disease see Section 16.3.2.9.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- **Cystic lesions**:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.2.3.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is

recommended that patients be excluded from trials where the main focus is on the ORR. Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.3.2.9.

16.2.4 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow-up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.

- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, Lactate Dehydrogenase (LDH) and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and SD (an effusion may be a side effect of the treatment) or PD (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.2.5 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target

lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.2.3.1.
- **Nodal target**: See Section 16.2.3.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on Electronic Case Report Form (eCRF).

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

16.2.6 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-3) and non-target lesions (Table 16-4) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-5) as well as the presence or absence of new lesions.

16.2.6.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

16.2.6.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are patient to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

16.2.6.1.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

16.2.6.2 Determination of target lesion response

Table 16-3 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]. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.2.4.)

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as PD
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-3 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of

diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.

- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
  - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
  - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
  - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an stable disease (SD) target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.2.6.3 Determination of non-target lesion response

Table 16-4 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[2].

[1]. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail

[2]. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify

equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK)
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.2.6.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.2.6.4 New lesions

The appearance of a new lesion is always associated with PD and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 16.2.7).

A **lymph node is considered as a "new lesion"** and, therefore, indicative of PD if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase. **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.2.4.

16.2.7 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-5.

Table 16-5 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 Section 16.2.6.

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

16.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.3.2.9 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.3.1 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.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, 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. If response assessments taken after

withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

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.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- -For non-randomized trials where response is the primary endpoint, confirmation is needed.
- -For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

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 or one determination of CR prior to progression where confirmation not 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 or one determination of PR prior to progression where confirmation not 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)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of ± 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline

at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR , or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with PD within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and 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 ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

16.3.2 Time to event variables

The protocol should state which of the following variables is used in that study.

16.3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

16.3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

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

16.3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If

a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

16.3.2.4 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

16.3.2.5 PFS2

A recent EMA guidance (EMA, 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of re-sensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments

16.3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter DoR but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of

responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if DoR is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

16.3.2.7 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the ORRs, since the same kind of selection bias may be introduced as described for DoR in Section 16.3.2.6. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

16.3.2.8 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

For all "time to event" variables, other than DoR, the randomization/ date of treatment start will be used as the start date.

For the calculation of DoR the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- 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.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.3.2.9).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.

- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

16.3.2.9 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 16-6.

Table 16-6 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 16.2.6.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as “responders” with respect to ORR and all other patients as “non-responders”.

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination

and/or timing of progression can incorporate data from patients with only non-measurable disease.

16.3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 16.3.2.8, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 16-7 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 16.3.2.8
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.3.2.8.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD

should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. 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 and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-7 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

16.4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

16.4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

16.4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 15 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Patient/guardian decision
- Death
- Progressive disease
- Any other protocol deviation that results in a significant risk to the patient’s safety
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment

Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which “*must*” lead to discontinuation of patient from trial.

In addition to the general withdrawal criteria, the following study specific criteria will also require study treatment discontinuation:

- Adjustments to study treatment due to toxicity that result in discontinuation. Please refer to Section 6.5.1 (for ribociclib treatment arm) and Section 6.5.3 (for combination chemotherapies arm).
- Use of prohibited medication. Please refer to Section 6.2.2.

16.4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Patient/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.4.5 Programming rules

The following should be used for programming of efficacy results:

16.4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

16.4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation 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 outlined in Section 16.3.2.8). 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.

16.4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

16.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

16.4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-7)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 16.3.2.8. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

16.5 References (available upon request)

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16.6 Appendix 3 – Patient Reported Outcomes FACT-B

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

16.7 Appendix 4 -Bone Marrow Reserve in Adults

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961

MARROW DISTRIBUTION OF THE ADULT

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head: Cranium Mandible	 165.8 16.4	 0.75 0.75	136.6 124.3 12.3	13.1	13.1
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle : 2 Humerus, head & neck 2 Scapulae 2 Clavicles	 26.5 67.4 21.6	 0.75 0.75 0.75	86.7 20.0 50.5 16.2	8.3	**8.3**
STERNUM AND RIBS	Sternum Ribs: 1 pair 2 3 4 5 6 7 8 9 10 11 12	39.0 10.2 12.6 16.0 18.6 23.8 23.6 25.0 24.0 21.2 16.0 11.2 4.6	0.6 All 0.4	23.4 82.6 4.1 5.0 6.4 7.4 9.5 9.4 10.0 9.6 8.5 6.4 4.5 1.8	2.3 7.9	**10.2**
PELVIC BONES	Sacrum 2 os coxae	194.0 310.6	0.75 0.75	145.6 233.0	13.9 22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		3.8