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Novartis Research and Development

LEE011

Clinical Trial Protocol CLEE011A2207 / NCT03822468

A phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of 400 mg of ribociclib in combination with non-steroidal aromatase inhibitors for the treatment of pre- and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who received no prior therapy for advanced disease

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List of abbreviations

aBC	advanced breast cancer
AE	adverse event
AESI	adverse events of special interest
AI	aromatase inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BC	breast cancer
BCRP	breast cancer resistance protein
BOR	Best Overall Response
BSEP	bile salt export pump
CABG	coronary artery bypass graft
CBP	childbearing potential
CBR	Clinical Benefit Rate
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulation
CI	confidence interval
CISH	chromogenic in situ hybridization
Cmax	maximum concentration
CMO & PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	central nervous system
CR	Complete Response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	coefficient of variation
CYP	cytochrome P450
DDE	direct data entry
DDI	drug-drug interaction
DHEA	Dehydroepiandrosterone
DILI	drug-induced liver injury
DOR	Duration of Response
EBV	Epstein–Barr virus

EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	End of Treatment
ER	estrogen receptor
eSAE	Electronic Serious Adverse Event
ET	endocrine therapy
EU	European Union
FAS	Full Analysis Set
FDG-PET	Flouro-deoxyglucose positron emission tomography
FISH	fluorescence in situ hybridization
FPFV	first patient first visit
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
GnRH	Gonadotropin-releasing hormone
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hormone receptor
HSV	herpes simplex virus
i.v.	intravenous
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
IHC	immunohistochemistry
IN	Investigator Notification
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase

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LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPLV	last patient last visit
LVEF	Left Ventricular Ejection Fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MI	myocardial infarction
MRI	Magnetic Resonance Imaging
MUGA	multiple gated acquisition
NaF PET	Sodium fluoride positron emission tomography
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NI	non-inferiority margin
NR	not reportable
NSAI	non-steroidal aromatase inhibitor
NTI	narrow therapeutic index
ORR	Overall Response Rate
OS	Overall Survival
p.o.	oral
PAS	Pharmacokinetic Analysis Set
PD	progressive disease
PET	positron emission tomography
PFS	Progression Free Survival
PgR	progesterone receptor
PK	pharmacokinetic(s)
PPS	Per-Protocol Set
PR	Partial Response
PT	Prothrombin time
QD	Quaque Die (every day)
QMS	Quality Management System
Rb	retinoblastoma
RFS	Recurrence-Free Survival
RoW	rest of world
s.c.	subcutaneous
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	Steering Committee
SD	stable disease
SEC	safety event categories
SGOT	serum glutamic oxaloacetic transaminase

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SGPT	serum glutamic pyruvic transaminase
SISH	silver in situ hybridization
SMQ	Standardized MedDRA Query
SOP	standard operating procedure
StD	standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBIL	total bilirubin
TdP	Torsades de Pointe
Tmax	The time at which the maximum observed concentration (Cmax) occurs
TTR	Time to Response
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
WBC	white blood cell(s)
WHO	World Health Organization
β-hCG	beta-human chorionic gonadotropin
Δ QTcF	change from baseline in QT interval in the ECG (corrected according to the formula of Fridericia)

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of patients fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and 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 patient, corresponding to a specific treatment arm assignment
Screen Failure	A patient who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Study drug/treatment	Any drug (or combination of drugs) administered to the patient as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.

Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient
Subject number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study
Treatment number	A unique identifier assigned in non-randomized studies to each dosed patient, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent (Woc)	Withdrawal of consent from the study is defined as when a patient 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, and does not allow analysis of already obtained biologic material

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Amendment 1 (24-Jan-2020)

Study CLEE011A2207 enrolled the first patient on 11-Jun-2019 and enrollment is currently ongoing with 125 patients in the study as of 24-Jan-2020.

Amendment rationale

The purpose of this amendment is to capture the new safety information and other changes included below.

- Interstitial Lung Disease (ILD)/pneumonitis has been observed across all CDK4/6 inhibitors treatment (Please refer to IB ed.14 for more information) therefore a new table - Table 6-6, 'Ribociclib dose adjustment and management recommendation for ILD/pneumonitis', has been added.
- Toxic Epidermal Necrolysis (TEN) has been reported in the post-marketing setting in a well-documented literature case report. No case was observed in the clinical trials. (Please refer to IB ed.14 for more information). The protocol section 6.3.1.4, Guidance for all other adverse reactions, has been updated with clear guidance to discontinue ribociclib if TEN is diagnosed.
- If a patient is on tamoxifen/toremifene, the following have been updated:
    - Included tamoxifen/toremifene as examples of neo-/adjuvant anti-cancer therapy that must be stopped for a washout period of 5 half-lives before randomization due to risk of QT prolongation (note to exclusion criterion 2).
    - Criteria for assessing post-menopausal status, in line with NCCN v4 2018 guidelines.
- Requirement for assessing sodium and phosphorus levels removed from inclusion criteria as abnormal sodium or phosphorus levels have no significant impact on QT prolongation.
- Concurrent Hormone Replacement Therapy (HRT) use added as an exclusion criterion due to its impact on breast cancer.
- Patients with named toxicities related to previous anticancer treatment that are not considered safety risks, allowed in to the study.
- Uncorrected hypocalcemia included to exclusion criterion 14 as one of the risks factors for QT prolongation.
- Guidance on corticosteroid use updated to be consistent with 'Concomitant medications' section.
- Guidance on contraception updated to indicate that hormonal contraceptives are not allowed due to their impact on breast cancer.
- For women who choose vasectomy of their male partner as the highly effective method of contraception, the requirement to medically confirm vasectomy added as per the current Clinical Trial Facilitation Group (CTFG) guidelines.
- Guidance updated on how to assess eligibility of patients participating in other medical research.

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- Lists of prohibited medications and medications to be used with caution during study drug treatment.
- Added the sample size justification for PK analysis.
- Other editorial changes throughout the document.

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.

- Section 5.1: Updated the following inclusion criteria:
    - 8: Removed sodium and phosphorus as laboratory values that must be within normal limits before first dose of study drug.
    - 13: Clarified contraception requirements. Vasectomy of male partners should be medically confirmed. Intrauterine systems (IUS) are not permitted.
    - 14: Clarified how to determine postmenopausal status for patients taking tamoxifen or toremifene and age <60.
- Section 5.2: Updated the following exclusion criteria:
    - 2: Clarified permitted prior neo-/adjuvant therapy with exemestane. Added neo-/adjuvant tamoxifen/toremifene as examples requiring a washout period of 5 half-lives before randomization due to risk of QT prolongation.
    - 6: Added exception, permitting patients with grade 1 taxane-induced neuropathy.
    - 7: Added exclusion of patients with 25% of the bone marrow previously irradiated.
    - 14: Added uncorrected hypocalcemia as an excluded risk factor for Torsades de Pointe (TdP).
    - 16: Clarified exclusion of patients participating in other studies involving investigational drugs and in any other type of medical research judged not to be scientifically or medically compatible with this study.
    - 17: Clarified exception that a short duration of systemic corticosteroids is permitted at any dose.
    - 18: Added criteria excluding patients concurrently using hormone replacement therapy.
- Table 6-1: Corrected provision of supplies to be either globally by sponsor or locally.
- Section 6.2.1.1.3: Added that cumulative courses of radiotherapy should not encompass >25% of irradiated bone marrow.
- Table 6-2: Corrected ribociclib capsules to ribociclib tablets.
- Table 6-6: Added ribociclib dose adjustment and management recommendations for ILD/pneumonitis.

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- Section 6.5.1.2: Clarified that ribociclib should be discontinued if TEN is diagnosed.
- Section 8.1: Clarified ECG evaluations used to determine eligibility can be repeated within the screening window for results out of the defined range before screen failing the patient.
- Section 8.4.2: Updated that ECG for eligibility assessment should be performed at least 72 hours before scheduled randomization date. Clarified that if QTcF value as the average of a triplicate ≥ 481 ms, study treatment must be interrupted, ECG repeated and management guidelines followed.
- Section 8.4.3: Clarified that FSH, estradiol, serum and urine pregnancy tests are to be performed locally.
- Section 8.5.1: Specified the number of evaluable patients required for the extensive PK analysis
- Section 12.7.3: Added the sample size justification of PK cohort.
- Table 16-1: List of prohibited medications updated.
- Table 16-2: List of medications to be used with caution updated.

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. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

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Protocol summary

Table 1 Protocol summary

Protocol number	**LEE011A2207**
Full Title	A phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of 400 mg of ribociclib in combination with non-steroidal aromatase inhibitors for the treatment of pre- and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who received no prior therapy for advanced disease
Brief title	Study of safety and efficacy of 400 mg of ribociclib in combination with non-steroidal aromatase inhibitors (NSAIs) in pre- and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who received no prior therapy for advanced disease
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	QT interval prolongation and neutropenia are considered to be important concentration dependent identified risks for ribociclib (Kisqali® Prescribing Information, Investigator Brochure). This study compares the currently approved dosing regimen of ribociclib 600 mg orally QD, 3 weeks on/1 week off in combination with NSAI (control arm) to ribociclib 400 mg orally QD, 3 weeks on/1 week off in combination with NSAI (experimental arm). The purpose of the study is to evaluate if the reduced dosing regimen of 400 mg ribociclib maintains efficacy of ribociclib in combination with an NSAI in pre- and postmenopausal women with HR-positive, HER2-negative aBC who have received no prior therapy for advanced disease while decreasing the risk of QTc prolongation. The risks of other AESI, such as neutropenia and hepatobiliary toxicity will be evaluated in this study as well.
Primary Objective(s)	The primary objective of this study is to determine whether the overall response rate (ORR) in the experimental arm (400 mg) is non-inferior to the control arm (600 mg) based on local tumor assessments (RECIST version 1.1) for all patients that have been treated for at least 6 months or have discontinued the study treatment.
Secondary Objectives	**Key secondary objective**: To evaluate QTc (with Fridericia's correction) prolongation in the experimental arm based on Δ QTcF at Cycle 1 Day 15 (at 2 h post-dose) **Other secondary objectives**: To evaluate each treatment arm with respect to: • Safety and tolerability based on frequency/severity of AEs including AEs of special interest (e.g. hepatobiliary toxicities, neutropenia), laboratory abnormalities, and the totality of ECG data observed including all post-baseline time points and the notable QTcF elevations • Progression-free survival (PFS), Clinical benefit rate (CBR), Time to response (TTR) and Duration of response (DOR) per RECIST 1.1 • Pharmacokinetics (PK) of ribociclib when given in combination with NSAI based on PK parameters such as Cmax, Tmax, and AUC0-24h for ribociclib

Study design	This is a phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of a reduced ribociclib dose of 400 mg in combination with an NSAI (letrozole or anastrozole) for the treatment of pre- and postmenopausal women with HR-positive, HER2-negative aBC who have received no prior therapy for advanced disease. Premenopausal women will also be receiving goserelin in both treatment arms. Patients will be randomly assigned to one of the below treatment arms in a 1:1 ratio: • Experimental arm (Arm 1) - Ribociclib 400 mg QD 3 weeks on/1 week off + NSAI (+ goserelin in premenopausal women) • Control arm (Arm 2) - Ribociclib 600 mg QD 3 weeks on/1 week off + NSAI (+ goserelin in premenopausal women) Randomization will be stratified by the presence of lung and/or liver metastases (yes versus no). In each stratum, patients will be randomly assigned to the experimental arm or the control arm in a 1:1 ratio.
Population	Pre- and postmenopausal women with HR-positive, HER2-negative advanced (i.e. loco-regionally recurrent or metastatic) breast cancer who have received no prior ET for advanced disease. Patients must be ≥ 18 years-old at the time of informed consent. Approximately 350 patients will be randomly assigned in a 1:1 ratio to either the Experimental (175 patients) or Control arms (175 patients).

Key Inclusion criteria	Refer to Section 5.1 for details on inclusion criteria.
	• Patient has advanced (loco-regionally recurrent or metastatic) breast cancer not amenable to curative therapy.
	• Patient has a histologically and/or cytologically confirmed diagnosis of ER-positive and/or PgR-positive breast cancer based on the most recently analyzed tissue sample, and all tested by local laboratory.
	• 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.
	• Patient must have measurable disease, i.e., at least one measurable lesion according to RECIST version 1.1. (a lesion in a previously irradiated site may only be counted as a target lesion if there is clear evidence of progression since the irradiation).
	• Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
	• Standard 12-lead ECG values defined as the mean of the triplicate ECGs and assessed by the central laboratory:
	  • QTcF interval at screening < 450 ms (QT interval using Fridericia's correction)
	  • Mean resting heart rate 50 to 90 bpm (determined from the ECG)
	• Women of childbearing potential (CBP), defined as all women physiologically capable of becoming pregnant, must have confirmed negative serum pregnancy test (for β-hCG) within 14 days prior to randomization.
	• Women of CBP must be willing to use highly effective methods of contraception.

Key Exclusion criteria	Refer to Section 5.2 for details on exclusion criteria. • Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's judgment. • Patient who received any prior systemic anti-cancer therapy (including endocrine therapy, chemotherapy, prior CDK4/6 inhibitors) for aBC. Patients who received neo-/adjuvant therapy for breast cancer are eligible. • Patient is concurrently using other anti-cancer therapy. • Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major toxicities. • Patient has received extended-field radiotherapy ≤ 4 weeks 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 has a concurrent malignancy or malignancy within 3 years of the randomization date, with the exception of adequately treated basal or squamous cell skin carcinoma, or curatively resected cervical carcinoma in situ. • Patients with central nervous system (CNS) involvement unless they meet specific stability criteria. • Patient has clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality. • Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, and has not fully recovered from side effects of such treatment.
Study treatment	"Study treatment" in this study refers to the combination of drugs and includes investigational drug (ribociclib) as well as NSAIs and goserelin. For this study, the term "investigational drug" refers to Novartis drug ribociclib (LEE011). The other drugs to be used in this study are NSAIs (letrozole or anastrozole) and premenopausal women will also be required to receive goserelin. Patients will be assigned at visit Cycle 1 Day 1 to one of the following two treatment arms: • Arm 1: Ribociclib 400 mg (2 x 200 mg tablets by mouth) QD on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (Days 22 to 28) + letrozole 2.5 mg by mouth QD continuously or anastrozole 1 mg by mouth QD continuously (+ goserelin 3.6 mg subcutaneously once every 4 weeks for premenopausal women) • Arm 2: Ribociclib 600 mg (3 x 200 mg tablets by mouth) QD on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (Days 22 to 28) + letrozole 2.5 mg by mouth QD continuously or anastrozole 1 mg by mouth QD continuously (+ goserelin 3.6 mg subcutaneously once every 4 weeks for premenopausal women)
Efficacy assessments	Efficacy assessments for the primary endpoint will include the following: • CT/MRI with contrast (Chest, Abdomen and Pelvis) every 8 weeks for the first 18 months, then every 12 weeks until 36 months and thereafter as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision (±7 days for all intervals).

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	• Brain CT or MRI as clinically indicated. • Whole body bone scan at screening if not collected previously within 42 days prior to randomization; as clinically indicated thereafter. • Bone x-ray, CT or MRI (if bone lesion at screening) every 8 weeks for the first 18 months and then every 12 weeks until 36 months and thereafter as clinically indicated (±7 days for all intervals). • Skin color photography (if skin lesions at screening) every 8 weeks during the first 18 months and then every 12 weeks until 36 months and thereafter as clinically indicated (±7 days for all intervals). • CT/ MRI for any disease outside of the chest, abdomen, pelvis (if lesion identified at screening) every 8 weeks for the first 18 months and then every 12 weeks until 36 months and thereafter as clinically indicated (±7 days for all intervals).
Key safety assessments	• Physical examinations • ECOG performance status • Height, weight, and vital signs • 12 lead Electrocardiograms • Laboratory assessments including hematology, chemistry, coagulation via International normalized ratio (INR) and pregnancy.
Pharmacokinetic assessments	• Blood collections for PK assessment of ribociclib will be obtained from all patients according to schedule of PK blood collection (Section 8.5.1.1.1). • In a subset of patients (~20 patients per arm), extensive PK blood sampling will be performed and samples will be collected as specified in Table 8-7. In all the remaining patients, PK samples will be collected matching the ECG measurement time points as specified in Table 8-8.
Data analysis	Refer to section 12 for details on data analysis and statistical methods. • The primary efficacy endpoint of the study is to evaluate the non-inferiority of Arm 1 compared to Arm 2, based on the ratio of ORR between the two arms based on local tumor assessment. The experimental arm (Arm 1) will be considered to be non-inferior to the control arm (Arm 2) if the lower 90% CI limit of the ratio of the ORR in Arm 1 to Arm 2 is > 0.814. The CI of ORR ratio will be constructed using Mantel-Haenszel method to include lung/liver metastasis as the stratification factor. The non-inferiority (NI) margin of 0.814 was chosen to demonstrate that ribociclib 400mg in combination with NSAI retains at least 50% of the treatment effect in terms of ORR of ribociclib 600mg in combination with NSAI vs. NSAI alone. • The Per-Protocol Set (PPS) is a subset of patients of the Full Analysis Set (FAS) without major protocol deviations. The PPS will be used for the analysis of the primary efficacy endpoint. • Other efficacy analyses including PFS, CBR, TTR and DOR will be analyzed using FAS which is comprised of all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to.

	• For the key secondary endpoint of the study, the objective of mitigating QT prolongation will be met if the upper 90% CI limit of the ΔQTcF at Cycle 1 Day 15 (2 h post-dose) in Arm 1 is less than 20 ms. Change from baseline of QTcF at other time points will also be summarized. Notable elevations of QTcF will be summarized based on all on-treatment ECG assessments. The totality of the safety data obtained in Arms 1 and 2, generated from each time point as outlined in the ECG monitoring and assessment schedule, will be compared as part of the overall assessment for QT prolongation risk mitigation. • The assessment of other safety endpoints will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. • The Safety Set 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/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received. • The Pharmacokinetic Analysis Set consists of all patients who received at least one dose of ribociclib and provide at least one evaluable PK concentration. PK parameters of ribociclib (and any relevant metabolites) will be listed by treatment and patient.
Key words	HR-positive, HER2-negative, ER-positive, PgR-positive, advanced breast cancer, ribociclib, NSAI, goserelin, letrozole, anastrozole, CDK4/6, Phase II, premenopausal and postmenopausal.

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1 Introduction

1.1 Background

1.1.1 Breast cancer epidemiology and current treatment landscape

Breast cancer (BC) is the most common form of cancer affecting women, accounting globally for 25% of all cancers and approximately 15% of all cancer deaths (Bray et al 2018).

It is a phenotypically diverse disease, the predominant subtype being the one whose tumor cells overexpress estrogen (ER) and/or progesterone (PgR) receptors. Approximately 70% of invasive breast cancers in women >50 years of age express ER and/or PgR, but not Human epidermal growth factor receptor 2 (HER2), and are termed hormone receptor-positive (HR-positive), HER2-negative (Howlader et al 2014).

Endocrine therapy (ET) is the core treatment modality for patients with HR-positive, HER2-negative advanced breast cancer (aBC) (NCCN guidelines, 2018). However, endocrine resistance eventually develops in virtually all patients and newer treatment modalities to overcome such resistance have been developed, such as the combined use of cyclin-dependent kinase (CDK) 4/6 inhibition and ET, leading to a substantially improved efficacy. Additionally, given that a substantial proportion of women with newly diagnosed aBC have few symptoms related to their cancer, measures to mitigate any increased treatment-related toxicity are important.

1.1.2 Role of the CDK4/6 pathway in BC

Dysregulation of the cyclin-dependent kinase (CDK)4/6-Retinoblastoma (Rb)- E2F pathway is an important contributor to ET resistance in BC. The luminal A and B subtypes of BC (85% of which are ER-positive and 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, Cancer Genome Atlas 2012, Cancer Genome Atlas 2012). Luminal A subtype tumors also have loss of CDKN2A, which encodes $p16^{INK4A}$, 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 may have clinical and therapeutic significance. For example, patients with HR-positive BC exhibiting a gene expression signature of Rb loss had a shorter recurrence-free survival (RFS) following adjuvant tamoxifen (Bosco et al 2007). A tumor gene expression signature of E2F activation is also associated with higher residual tumor cell proliferation following neoadjuvant aromatase inhibitor (AI) therapy. Therefore, activation of the CDK4/6-Rb-E2F pathway promotes endocrine resistance, and treatment with a CDK4/6 inhibitor or knockdown of CDK4 expression leads to reactivation of Rb, binding back of E2F and subsequent cell cycle arrest, thus abrogating endocrine-resistant cell proliferation.

Selective inhibitors of CDK4/6, such as palbociclib, abemaciclib and ribociclib, demonstrated synergy with ET in preclinical studies and efficacy in clinical studies and have been approved as initial therapy (in combination with an AI) or after disease progression following prior ET (in combination with fulvestrant) in patients with HR-positive, HER2-negative aBC

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(Turner et al 2015, Loibl et al 2016, Goetz et al 2017, Hortobagyi et al 2016, Slamon et al 2018, Finn et al 2016) (refer to the current ribociclib Investigator's Brochure (IB) and the current Kisqali® prescribing information for more information about the efficacy of ribociclib).

Considering the demonstrated efficacy of CDK4/6 inhibitors in combination with endocrine therapy in the treatment of both pre and postmenopausal patients with HR-positive, HER2-negative aBC, 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 resistance in both pre and postmenopausal women.

1.1.3 Overview of Investigational Treatment and Other Trial Treatments

This study includes treatment with ribociclib (LEE011) and ET using non-steroidal aromatase inhibitors (NSAI: anastrozole or letrozole) +/- goserelin (in premenopausal women only).

1.1.3.1 Overview of Ribociclib

Ribociclib is an orally bioavailable and highly selective small molecule inhibitor with highly specific nanomolar inhibitory activity against the CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes.

In the United States, Ribociclib (Kisqali®) has been approved by the United States Food and Drug Administration (U.S. FDA) in combination with:

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

In EU, Ribociclib (Kisqali®) has been approved by the European Commission as an initial ET for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic BC in combination with an AI.

1.1.3.1.1 Clinical experience

Ribociclib is being investigated in patients with BC and other solid tumors in multiple clinical trials at different phases of development. Three large phase III studies in patients with aBC have led to regulatory approvals as detailed above.

1.1.3.1.2 Clinical safety

Clinical safety of ribociclib with endocrine agents such as letrozole, tamoxifen, exemestane, fulvestrant, and goserelin has been evaluated in several combination trials. The safety profile of ribociclib in combination with NSAI (+/- goserelin) was investigated in two phase III trials in aBC (MONALEESA-2 [CLEE011A2301] and MONALEESA-7 [CLEE011E2301]). Important identified risks for ribociclib treatment include corrected QT (QTc) interval prolongation, hepatotoxicity, and myelosuppression, mainly neutropenia.

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In a pooled dataset of patients treated with ribociclib plus NSAI in MONALEESA-2 (CLEE011A2301), MONALEESA-7 (CLEE011E2301) and the phase II study CLEE011X2107 (n=629), 4.7% and 1.0% of patients had at least one post-baseline ECG showing QTcF > 480 ms and > 500 ms, respectively. The corresponding frequencies were 0.9% and 0% in patients in the placebo plus NSAI group (n=577). Furthermore, 5.0% of patients treated with ribociclib plus NSAI had at least one episode of > 60 ms QTcF prolongation compared with 0.2% in patients treated with placebo plus NSAI. The proportion of patients with hepatobiliary toxicity events was also higher in ribociclib group than the placebo group (24.6% vs. 17.2%). The most frequently reported events in this category included increased ALT (16.1% vs. 6.4%) and increased AST (15.3% vs. 6.9%). Additionally, any grade neutropenia occurred in 78.2% of patients treated with ribociclib plus NSAI, compared with 6.6% of patients in the pool treated with placebo plus NSAI. Febrile neutropenia was reported in 1.6% and 0.3% of patients respectively.

Irrespective of grade and causality, the AEs experienced by a higher proportion (with ≥ 10% difference) of patients in the ribociclib plus NSAI group (n=629) compared to the placebo plus NSAI group (n=577) included: neutropenia (+56.9%), decreased neutrophil count (+24.3%), nausea (+18.3%), decreased WBC count (+15.0%), alopecia (+13.7%), anemia (+13.6%), and leukopenia (+13.2%).

For a comprehensive review of the safety profile of ribociclib in combination with endocrine agents, please refer to the current ribociclib IB and Kisqali® prescribing information, as appropriate.

1.1.3.1.3 Clinical efficacy

Efficacy of ribociclib with endocrine agents has been evaluated in three published phase III combination trials in patients with aBC, two of them evaluating the combination of ribociclib with NSAI (+/- goserelin).

MONALEESA-2 (CLEE011A2301) is a phase III, double-blind, placebo-controlled, multicenter study of the combination of ribociclib or placebo with letrozole in postmenopausal women with HR-positive, HER2-negative aBC who have not received prior therapy for their advanced disease. The study met its primary objective at a pre-specified interim analysis where ribociclib in combination with letrozole demonstrated statistically significant benefit over placebo in combination with letrozole in prolonging investigator-assessed progression free survival (PFS); (Hazard ratio = 0.556, 95% CI: 0.429, 0.720; one sided p-value = 3.29×10^{6}). An updated PFS analysis performed approximately 12 months later, demonstrated continued efficacy of ribociclib, with the median PFS prolonged by 9.3 months, from 16.0 months in the placebo with letrozole arm to 25.3 months in the ribociclib with letrozole arm. While the overall survival (OS) data was still immature at time of the updated PFS analysis, there was numerically lower number of deaths in the ribociclib with letrozole arm compared to the placebo with letrozole arm.

Similarly, MONALEESA-7 (CLEE011E2301) is a randomized double-blind phase III study of ribociclib or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of pre- and perimenopausal women with HR-positive, HER2-negative, aBC who received no prior hormonal therapy for advanced disease. The study met its primary endpoint by increasing median PFS (per investigator

[redacted]

assessment) from 13.0 months (95% CI: 11.0 to 16.4) with placebo to 23.8 months (95% CI: 19.2 - NR) with ribociclib ($P = 9.83 \times 10^{-8}$; hazard ratio = 0.55; 95% CI: 0.44 - 0.69). The results were consistent in the subgroup of patients who received NSAI as endocrine combination partner with a 43.1% relative risk reduction (hazard ratio = 0.569; 95% CI 0.436, 0.743) and a 13.7-month prolongation in median PFS.

Please, refer to the current ribociclib IB and Kisqali® prescribing information for additional details on the efficacy profile of ribociclib.

1.1.3.1.4 Clinical Pharmacokinetics of Ribociclib

The clinical pharmacokinetics (PK) of ribociclib have been evaluated in a phase I study in patients with advanced solid tumors or lymphomas (CLEE011X2101). Following repeated daily oral administration, steady-state of ribociclib was achieved by approximately Day 8. LEQ803, an active metabolite of ribociclib, has similar PK characteristics as the parent drug. 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 (CLEE011A2102). 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) following ribociclib treatment 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 (ritonavir) increased ribociclib AUC by 3.2-fold following a single oral dose of 400 mg ribociclib (CLEE011A2101). Co-administration of a strong CYP3A4 inducer (rifampicin) decreased ribociclib AUC_{inf} 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 midazolam (CYP3A4 substrate) with multiple doses of ribociclib (400 mg) increased midazolam exposure by 3.8-fold. Co-administration of caffeine (CYP1A2 substrate) with multiple doses of ribociclib (400 mg) increased caffeine exposure 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 interaction (DDI).

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, CLEE011A2103).

No apparent drug-drug interaction (DDI) was observed between ribociclib and the combination partner letrozole or anastrozole based on PK data in the MONALEESA-2 and -7 trials. Based

on the population PK analysis, concomitant use of letrozole or anastrozole had no impact on ribociclib exposure.

Refer to the current ribociclib IB and Kisqali® prescribing information for additional details.

1.1.3.2 Overview of Non-steroidal Aromatase Inhibitors (NSAIs) and GnRH agonists

The following sections provide general information on Letrozole and Anastrozole (NSAIs) and goserelin (GnRH agonist). Refer to the current local prescribing information and local clinical guidelines for comprehensive safety and efficacy information and guidance for each medication.

1.1.3.2.1 Overview of Letrozole

Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system. Letrozole acts by highly selective inhibition of the conversion of androgens (mainly from adrenal glands, the primary source of estrogens in postmenopausal women) to estrogens. Letrozole induces a 75% to 95% decrease of estrogen levels after two weeks of treatment with daily doses of 0.1 to 5 mg, with no significant clinical and laboratory toxicities or changes in levels of other hormones.

Letrozole is administered orally once daily at a dose of 2.5 mg. It is rapidly and completely absorbed from the GI tract. Concomitant intake of food has no effect on the extent of its absorption. Letrozole is metabolized via CYP3A4 to a pharmacologically-inactive metabolite and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance.

Letrozole (2.5 mg daily) and ribociclib (600 mg daily, 3 weeks on/1 week off) did not affect metabolism of each other in a phase Ib/II dose escalation/expansion study (CLEE011X2107).

The most frequently reported adverse events (AE) for letrozole in clinical trials were hot flushes, arthralgia/arthritis and myalgia. In the first line setting, the most frequently reported adverse events include musculoskeletal pain (bone/back pain and arthralgia), hot flushes, nausea and dyspnea. In general, the observed adverse reactions are mild to moderate in nature.

Refer to the current local prescribing information for more information on letrozole.

1.1.3.2.2 Overview of Anastrozole

Anastrozole, like letrozole, is a selective NSAI. It significantly lowers serum estradiol concentrations with no detectable effect on the formation of adrenal corticosteroids or aldosterone.

Anastrozole is administered orally once daily at a dose of 1 mg, taken with or without food. Anastrozole is metabolized by N-dealkylation, hydroxylation and glucuronidation. Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Renal elimination accounts for approximately 10% of total clearance. The major circulating metabolite of anastrozole lacks pharmacologic activity. Anastrozole metabolism occurs mainly via CYP3A4 and UGT1A4 based on *in vitro* data. Therefore, anastrozole metabolism may potentially be affected by co-administration with ribociclib. However, anastrozole has been studied up to doses of 10 mg/day (10-times daily dose) and all doses evaluated were well tolerated with no

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serious acute toxicities attributed to anastrozole. Additionally, no evidence of a PK interaction between ribociclib and anastrozole was observed in MONALEESA-7 (CLEE011E2301).

Refer to the current local prescribing information for more information on anastrozole.

1.1.3.2.3 Overview of Goserelin

GnRH agonists are synthetic analogues of gonadotropin-releasing hormone that by continuous stimulation of the GnRH receptor achieve desensitization of the pituitary gland to GnRH. GnRH agonists differ from the naturally-occurring GnRH by modifications in the decapeptide structure (usually by amino acid substitution in position 6, but also in positions 9 and 10) to decrease degradation of the molecule.

Goserelin is the GnRH agonist to be used in this study. Goserelin is administered subcutaneously every 28 days at a dose of 3.6 mg. Following subcutaneous administration of goserelin (3.6 mg for 2 months), Tmax was 8 to 22 days post-dose in female subjects. The most common AEs occurring in women treated with goserelin include hot flushes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea and peripheral edema.

The metabolism of goserelin is not CYP-mediated; rather hydrolysis of C-terminal amino acids is the major clearance mechanism. No formal clinical DDI studies have been conducted or reported with goserelin. Based on the available information, no DDI between goserelin and ribociclib is expected (Zoladex® Prescribing Information).

Refer to the current local prescribing information and/or clinical guidelines for more information on goserelin.

1.2 Purpose

QT interval prolongation and neutropenia are considered to be important identified risks for ribociclib (Kisqali® Prescribing Information, Investigator Brochure). The approved dosing regimen of ribociclib (Kisqali®) is 600 mg daily (QD) on a 3 weeks on/1 week off schedule.

The purpose of the study is to explore a reduced dosing regimen of 400 mg ribociclib orally QD 3 weeks on/1 week off that may decrease the risk of QTc prolongation without compromising the efficacy of ribociclib in combination with an NSAI in pre- and postmenopausal women with HR-positive, HER2-negative aBC who have received no prior therapy for advanced disease. The risks of other AEs of special interest, such as neutropenia and hepatobiliary toxicity will be evaluated in this study as well.

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2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To determine whether the overall response rate (ORR) in the experimental arm is non-inferior to the control arm.	• ORR is based on local tumor assessments (RECIST version 1.1) for all patients that have been treated for at least 6 months or have discontinued the study treatment.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Key secondary objective:** To evaluate QTc (with Fridericia's correction) prolongation in the experimental arm	• **Key Secondary endpoint:** Δ QTcF at Cycle 1 Day 15 (at 2h post-dose)
• **Other Secondary objectives:** To evaluate each treatment arm with respect to:	• **Other Secondary endpoints:**
• Safety and tolerability (including hepatobiliary toxicities and neutropenia)	• Frequency/ severity of AEs, including AEs of special interest (e.g. hepatobiliary toxicities, neutropenia) Laboratory abnormalities Summary of Δ QTcF at timepoints other than Cycle 1 Day 15 (at 2hr post-dose) ECG notable values based on all post baseline assessments.
• Progression-free survival (PFS)	• PFS per RECIST 1.1
• Clinical benefit rate (CBR)	• CBR per RECIST 1.1
• Time to response (TTR)	• TTR per RECIST 1.1
• Duration of response (DOR)	• DOR per RECIST 1.1
• Pharmacokinetics (PK) of ribociclib when given in combination with NSAI	• PK parameters such as Cmax, Tmax, and AUC0-24h for ribociclib

3 Study design

This is a phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of a reduced starting ribociclib dose of 400 mg in combination with an NSAI (letrozole or anastrozole) for the treatment of pre- and postmenopausal women with HR-positive, HER2-negative aBC who have received no prior therapy for advanced disease. Premenopausal women will also be required to receive goserelin in both treatment arms.

Approximately 350 patients will be randomly assigned to one of the below treatment arms in a 1:1 ratio (Figure 3-1):

- Experimental arm (Arm 1) - Ribociclib 400 mg QD 3 weeks on/1 week off + NSAI (+ goserelin in premenopausal women): 175 patients
- Control arm (Arm 2) - Ribociclib 600 mg QD 3 weeks on/1 week off + NSAI (+ goserelin in premenopausal women): 175 patients

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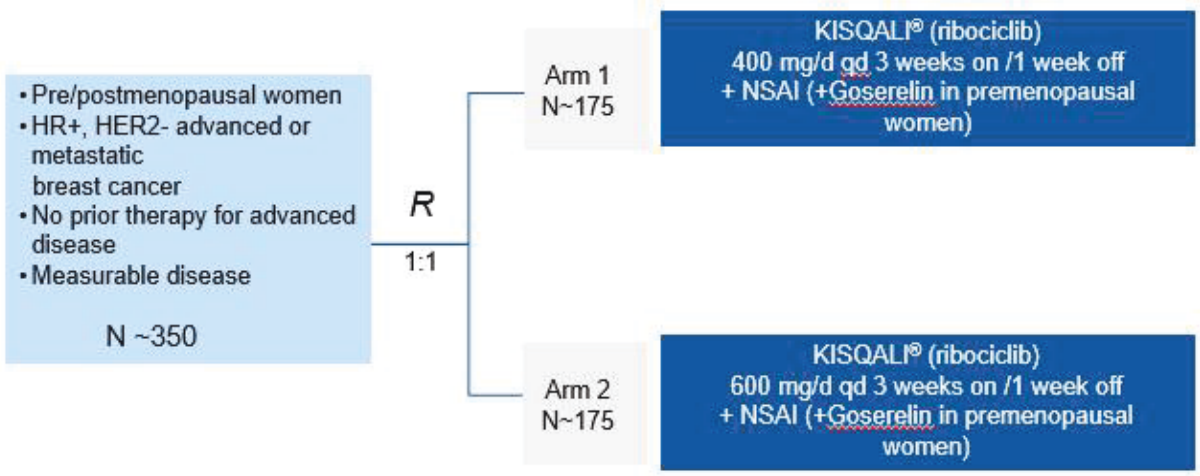
Randomization will be stratified by the presence of lung and/or liver metastases (yes versus no).

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

This study compares the currently approved dosing regimen of ribociclib 600 mg orally QD, 3 weeks on/1 week off to ribociclib 400 mg orally QD, 3 weeks on/1 week off.

The study will include pre- and postmenopausal women with hormone receptor-positive, HER2-negative aBC who received no prior therapy for advanced disease that will be randomized in a 1:1 ratio to the control and experimental arms.

The inclusion of a control arm (600 mg) is necessary in order to provide a contemporaneous comparator for assessment of efficacy, ΔQTcF and other descriptive comparisons. The 400 mg dosing regimen in the experimental arm is expected to maintain an efficacy benefit in patients with HR-positive, HER2-negative metastatic BC, with the potential for an improved safety profile by reducing QTcF prolongation and frequency of other AEs such as neutropenia.

The two-arm randomized design minimizes allocation bias, balancing both known and unknown prognostic factors in the assignment of treatments. Randomization is stratified by lung and/or liver involvement (yes versus no). This stratification factor was selected because of its well-recognized prognostic value in aBC. The primary analysis will be conducted when patients have been treated for at least 6 months from randomization or have discontinued study treatment. This is based on data from the MONALEESA-2 (CLEE011A2301) study that show that the majority of responses occur within this timeframe.

4.2 Rationale for dose/regimen and duration of treatment

Clinical studies show that ribociclib-induced QTcF interval prolongation is concentration-dependent (current ribociclib IB and Kisqali® prescribing information).

Based on pharmacokinetic (PK)-QTcF modeling, the 400 mg dose of ribociclib is estimated to result in a lower mean ΔQTcF (Table 4-1).

Table 4-1 Estimated Cmax and mean QTcF change from baseline at different dose regimens of ribociclib

Ribociclib dosing regimen	Estimated geometric mean Cmax (ng/mL)	Estimated mean ΔQTcF (ms) (90% CI) of ribociclib + NSAI[a]
600 mg QD 3 weeks on/1 week off (approved dosing regimen)	1870	22.6 (21.06, 24.06)
400 mg QD 3 weeks on/1 week off	1080	18.9 (17.65, 20.11)

[a] Estimated by PK-QT model based on the pop-PK model predicted Cmax,ss. Both models were developed based on data from studies CLEE011X2101, CLEE011X1101, CLEE011X2107, CLEE011A2301, CLEE011E2301 and CLEE011F2301. In MONALEESA-2 (CLEE011 A2301) observed ΔQTcF was 19.6 ms (90% CI: 18.0, 21.2).

Neutropenia is another important identified risk of ribociclib. In the Kisqali® prescribing information, ribociclib dose modification recommendations are provided for managing neutropenia based on the severity grade as per Common Terminology Criteria for Adverse Events (CTCAE). To assess the impact of the proposed 400 mg dose on neutropenia, modeling was performed for the parameter absolute neutrophil count (ANC) at different dosing regimens of ribociclib. Simulation of ANC profiles shows that ribociclib 400 mg QD leads to a smaller ANC decrease than the 600 mg QD dose (Figure 4-1).

Hepatobiliary toxicity, mostly manifested as transient increases in serum transaminases levels, is also an important identified risk of ribociclib, and dose modification recommendations are provided for its management in the prescribing information (Kisqali® Prescribing Information). While simulation of hepatotoxicity at different doses of ribociclib was not performed due to low numbers of events of this toxicity and no relationship has yet been observed between ribociclib exposure and serum transaminases increases (data from MONALEESA-2), it is reasonable to presume that the incidence and severity of this toxicity may also decrease with a lower daily dose of ribociclib, thus potentially contributing to a better overall safety profile.

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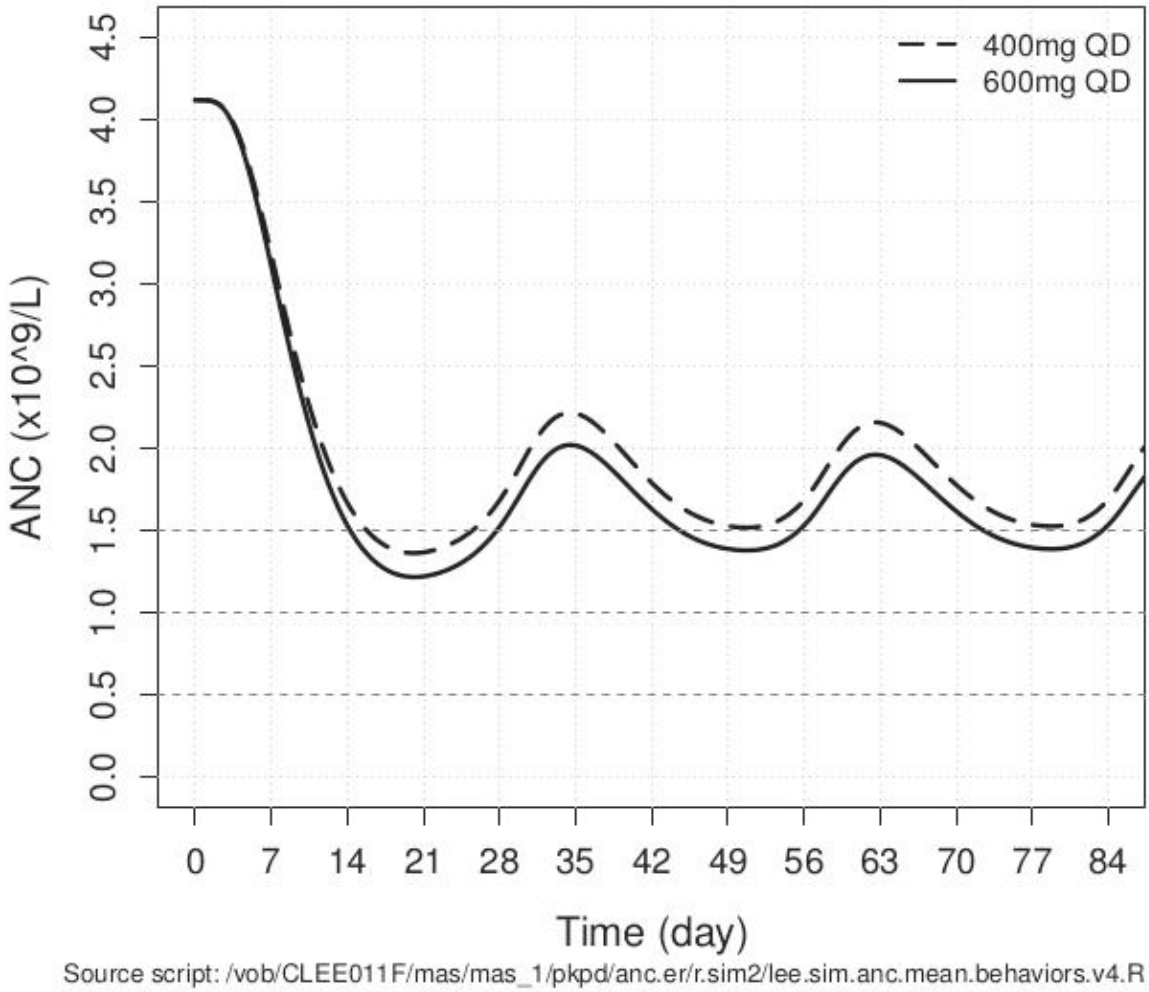
Figure 4-1 Simulated absolute neutrophil count (ANC) mean profiles at different regimens of ribociclib



Note: Mean ANC profiles are predicted by the ANC exposure-response model developed based on data from studies CLEE011X2101, CLEE011X1101, CLEE011X2107, CLEE011A2301, CLEE011E2301 and CLEE011F2301.

With regards to efficacy, post-hoc exploratory analyses of studies MONALEESA-2 (CLEE011A2301), MONALEESA-3 (CLEE011F2301) and MONALEESA-7 (CLEE011E2301) suggest that patients who started ribociclib at 600 mg but had their dose reduced (e.g. due to AE) to 400 mg and 200 mg continued to experience treatment benefit, in terms of PFS and ORR .While these observations should be interpreted with caution due to the potential confounding factor of the 600 mg QD starting dose, they do provide insights regarding the potential effectiveness of lower ribociclib dose regimens.

Supporting this, there was no clear relationship between ribociclib exposure and efficacy endpoints based on exposure-efficacy analysis in either MONALEESA-7 or MONALEESA-3 as well as in a pooled analysis of MONALEESA-2, MONALEESA-7 and MONALEESA-3.

In the exposure-efficacy analysis in each of MONALEESA-7 and MONALEESA-3, no clear relationship was observed between Ctrough_avg_ss quartile (geometric mean of Ctrough values

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from C1D15 and C3D15 concentrations for MONALEESA-7 and C2D15 for MONALEESA-3) and PFS or TTR in patients treated with ribociclib. In addition, there was no clear relationship between ribociclib exposure and efficacy from pooled population PK analyses.

In summary, based on the PK-QTcF modeling, exploratory PFS and ORR analyses, and supported by the PK-ANC modeling, the 400 mg total daily dose of ribociclib may be associated with less toxicity (e.g. lower ΔQTcF, lower incidence of neutropenia and possibly other adverse events) than the 600 mg daily dose, while potentially maintaining efficacy. Therefore, the ribociclib dosing regimen of 400 mg QD 3 weeks on/ 1 week off will be explored in patients with HR-positive, HER2-negative aBC in this study.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The control arm is ribociclib 600 mg QD 3 weeks on/1 week off on a 28-day cycle in combination with an NSAI (letrozole or anastrozole) and goserelin (for pre-menopausal women only), according to the approved Kisqali® label (prescribing information). The efficacy and toxicity of the control arm regimen have been assessed in Phase III studies that have led to regulatory approval of the regimen for this patient population. It represents one of the preferred treatment options in this patient population according to international guidelines (NCCN guidelines 2018, Cardoso et al 2018) and it is an appropriate contemporaneous comparator for the experimental arm.

4.4 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned for this study. Refer to Section 12.6.

4.5 Risks and benefits

Based on clinical data, treatment of ribociclib in combination with NSAI is expected to be tolerable and toxicities of the treatment are expected to be manageable and reversible with treatment interruption, ribociclib dose reduction, or discontinuation. The 600 mg dose of ribociclib in combination with an NSAI has been investigated in the MONALEESA-2 and MONALEESA-7 Phase III studies in post- and premenopausal women with aBC respectively (see Section 1.1.3.1.2 and Section 1.1.3.1.3 for a summary of safety and efficacy respectively). Further details can be found in the prescribing information. Less toxicity is expected in Arm 1 compared to Arm 2, given the decreased ribociclib dose, with the study aiming to demonstrate that this can be achieved while maintaining efficacy.

Patients in this study will be carefully monitored for key toxicities that have been observed with ribociclib (refer to the current ribociclib IB and Kisqali® prescribing information, as appropriate) and risks will be further minimized by adherence to inclusion/exclusion selection criteria (Section 5), avoidance of prohibited medications (Section 6.2.2), close safety monitoring (Section 10) and dose modification guidelines (Section 6.5).

As per the inclusion/exclusion selection criteria, 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 must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the inclusion criteria. If there is any

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question that the patient will not reliably comply, they should not be entered or continue in the study.

A Steering Committee (SC) will be established and it will be comprised of investigators and Novartis personnel participating in the trial, to ensure transparent management of the study according to the protocol through recommending and approving modifications as outlined in Section 10.2.1.

5 Population

Pre- and postmenopausal women with HR-positive, HER2-negative advanced (i.e. loco-regionally recurrent or metastatic) breast cancer who have received no prior ET for advanced disease. 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. Signed informed consent must be obtained prior to any screening procedures.
2. Patient is an adult female ≥18 years-old at the time of informed consent.
3. Patient has advanced (loco-regionally recurrent or metastatic) breast cancer not amenable to curative therapy.
4. Patient has a histologically and/or cytologically confirmed diagnosis of ER-positive and/or PgR-positive breast cancer based on the most recently analyzed tissue sample, and all tested by local laboratory.
5. 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.
6. Patient must have measurable disease, i.e., at least one measurable lesion according to RECIST version 1.1. (a lesion in a previously irradiated site may only be counted as a target lesion if there is clear evidence of progression since the irradiation).
7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
8. Patient has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory for eligibility):
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    - Platelets $\geq 100 \times 10^9$/L
    - Hemoglobin ≥ 9.0 g/dL
    - INR ≤ 1.5 (unless the patient is receiving anticoagulants and the INR is within the therapeutic range of intended use for that anticoagulant within 7 days prior to the first dose of study drug).
    - Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) formula
    - Total bilirubin < ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is $\leq 3.0 \times$ ULN or direct bilirubin $\leq 1.5 \times$ ULN.

[redacted]

- Aspartate transaminase (AST) < 2.5 × ULN, except for patients with liver metastases, who are only included if the AST is <5 × ULN.
- Alanine transaminase (ALT) < 2.5 × ULN, except for patients with liver metastases, who are only included if the ALT is < 5 × ULN.
- Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements (the central laboratory value should be documented within normal limits after the correction) before the first dose of study drug:
  - Potassium
  - Magnesium
  - Total calcium (corrected for serum albumin)

9. Standard 12-lead ECG values defined as the mean of the triplicate ECGs and assessed by the central laboratory:
   - QTcF interval at screening < 450 ms (QT interval using Fridericia's correction)
   - Mean resting heart rate 50-90 bpm (determined from the ECG)
10. Patient must be able to swallow ribociclib tablets.
11. Patient must be able to communicate with the investigator and comply with the requirements of the study procedures.
12. Women of childbearing potential (CBP), defined as all women physiologically capable of becoming pregnant, must have confirmed negative serum pregnancy test (for β-hCG) within 14 days prior to randomization.
13. Women of CBP must be willing to use highly effective methods of contraception. Contraception must continue 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.
    - Female sterilization - surgical bilateral oophorectomy with or without hysterectomy, total hysterectomy or bilateral tubal ligation at least 6 weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. See the definition of CBP below for more information.
    - Male partner sterilization (at least 6 months prior to randomization). For patients on the study, the vasectomized male partner should be the sole partner for that patient and the vasectomy must be medically confirmed as per local practice.
    - Placement of an intrauterine device (IUD).

    Notes:
    - 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.
    - Women are considered of CBP unless: they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate,

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history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks prior to randomization. In the case of oophorectomy alone, only after the reproductive status of the woman has been confirmed by follow-up hormone level assessment, is she considered not of CBP.

14. Patient has a known menopausal status at the time of informed consent form (ICF) signature. Patient is considered postmenopausal if: i) she has had prior bilateral oophorectomy; ii) is age ≥ 60 years; iii) is age <60 years and has had amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and follicle stimulating hormone (FSH) and estradiol in the postmenopausal range per local normal ranges; iv) if taking tamoxifen or toremifene and age <60, then FSH and plasma estradiol level in postmenopausal range. (NCCN v15 2018). All other patients who do not meet the criteria for postmenopausal status are considered premenopausal and must receive goserelin in addition to the NSAI.
15. 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 with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's judgment.
2. Patient who received any prior systemic anti-cancer therapy (including endocrine therapy, chemotherapy, prior CDK4/6 inhibitors) for aBC.

   Note:

   - Patients who received neo-/adjuvant therapy for breast cancer are eligible. Neo-/adjuvant therapy with letrozole, anastrozole, or exemestane must be stopped at least 12 months prior to the date of randomization. Prior neo-/adjuvant therapy with CDK4/6 inhibitors is not permitted.
   - Any other prior neo-/adjuvant anti-cancer therapy (e.g. tamoxifen or toremifene) must be stopped at least 5 half-lives or 7 days, whichever is longer, before the date of randomization.
   - Patients who received 14 or less days of letrozole or anastrozole for advanced disease prior to the date of randomization are eligible.
   - Patients who received 28 days or less of goserelin for advanced disease prior to the date of randomization are eligible. Patients who are receiving goserelin for reasons other than aBC (e.g. endometriosis or as adjuvant treatment) are also eligible.
3. Patient with a known hypersensitivity to any of the excipients of ribociclib (eg. ribociclib tablets coating contains soya lecithin, and therefore should not be taken by patients who are allergic to peanuts or soya), letrozole or anastrozole or goserelin (premenopausal women only).
4. Patient is concurrently using other anti-cancer therapy.
5. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major toxicities.

[redacted]

6. Patient has not recovered from acute clinical and laboratory toxicities related to prior anticancer therapies to NCI CTCAE v4.03 grade ≤ 1 (except for patients with grade 1 taxane-induced neuropathy, any grade of alopecia, amenorrhea or other toxicities not considered a safety risk for the patient at investigator's discretion).
7. Patient has received extended-field radiotherapy ≤ 4 weeks 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). Patients in whom ≥ 25% (Ellis 1961) of the bone marrow has been previously irradiated are also excluded.
8. Patient has a concurrent malignancy or malignancy within 3 years of the randomization date, with the exception of adequately treated basal or squamous cell skin carcinoma, or curatively resected cervical carcinoma *in situ*.
9. Patient has a history of HIV infection (testing is not mandatory unless required by local regulations).
10. Patient has active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (testing is not mandatory unless required by local regulations).
11. Patients with central nervous system (CNS) involvement unless they meet the following two criteria:
    - At least 4 weeks have elapsed from CNS-directed prior therapy completion (e.g. including radiation and/or surgery) to study treatment start.
    - Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
12. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., uncontrolled ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
13. Patient has any other concurrent severe and/or uncontrolled medical condition that would in the investigator's judgment, cause unacceptable safety risks to the patient, contraindicate patient participation in the clinical study, or compromise compliance with the protocol.
14. Patient has clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, including any of the following:
    - History of documented myocardial infarction (MI), angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction (LVEF) < 50% as determined by the multiple gated acquisition (MUGA) scan or echocardiogram (testing is not mandatory)
    - 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

[redacted]

- 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, whichever is longer)
- 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 (SBP) >160 or <90 mmHg

15. 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, pomelos, 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.
16. 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.
17. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, and has not fully recovered from side effects of such treatment.
    Note: The following uses of corticosteroids are permitted:
    - 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).
    - A short duration (< 5 days) of systemic corticosteroids.
18. Pregnant or breast-feeding (lactating) women or women who plan to become pregnant or breast-feed during the study.
19. Patient is concurrently using hormone replacement therapy.

6 Treatment

6.1 Study treatment

"Study treatment" in this study refers to the combination of drugs and includes investigational drug (ribociclib) as well as NSAIs and goserelin.

The term "investigational drug" refers to Novartis drug ribociclib (LEE011). The other drugs to be used in this study are NSAIs (letrozole or anastrozole) and goserelin.

Ribociclib (LEE011) will be supplied by Novartis or its designee in the form of 200 mg tablets as individual patient supply packaged bottles. Letrozole, anastrozole, and goserelin will be procured locally as they are commercially available in each participating country according to

[redacted]

local practices and regulations. Storage conditions are described in the medication labels. Medication labels will comply with the legal requirements of each 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 eCRF.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and combination drug

Investigational/ Combination Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Global or Local
Ribociclib (LEE011) 200 mg	Tablet	Oral use	Open label patient specific supply; Bottle	Sponsor - Global
Letrozole 2.5 mg	Tablet	Oral use	Open label patient packs	Local
Anastrozole 1 mg	Tablet	Oral use	Open label patient packs	Local
Goserelin 3.6 mg	Implant, in pre-filled syringe	Subcutaneous use	Open label patient packs	Local

6.1.2 Additional study treatments

No other treatments beyond ribociclib and endocrine therapy (NSAI +/- goserelin) are included in this study.

6.1.3 Treatment arms/group

Patients will be assigned at visit Cycle 1 Day 1 to one of the following two treatment arms in a ratio of 1:1.

- **Arm 1:**
  - Ribociclib 400 mg (2 x 200 mg tablets by mouth) QD on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (Days 22 to 28).

in combination with:

Endocrine therapy consisting of:

- For **postmenopausal** women:
  - Letrozole 2.5 mg by mouth QD continuously or anastrozole 1 mg by mouth QD continuously.
- For **premenopausal** women:
  - Letrozole 2.5 mg by mouth QD continuously or anastrozole 1 mg by mouth QD continuously, combined with:
  - Goserelin 3.6 mg subcutaneously once every 4 weeks.

[redacted]

- **Arm 2:**
  - Ribociclib 600 mg (3 x 200 mg tablets by mouth) QD on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (Days 22 to 28).

in combination with

Endocrine therapy consisting of:

- For **postmenopausal** women:
  - Letrozole 2.5 mg by mouth QD continuously or anastrozole 1 mg by mouth QD continuously.
- For **premenopausal** women:
  - Letrozole 2.5 mg by mouth QD continuously or anastrozole 1 mg by mouth QD continuously, combined with:
  - Goserelin 3.6 mg subcutaneously once every 4 weeks.

Ribociclib, letrozole, anastrozole, and goserelin will be administered as a flat-fixed dose, and not by body weight or body surface area. The choice of letrozole or anastrozole is at the Investigator's discretion but switching from one to the other while on the study, is not allowed.

The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site during their next scheduled visit. The site personnel will ensure that the appropriate dose of each study drug is provided at each scheduled visit.

6.1.3.1 General dosing guidelines

The study treatment should be taken as follows:

- Ribociclib is dosed for the first 21 days out of the 28 day cycle.
- On scheduled visit days, patients must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days patients may take study treatment at home.
- 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. Up to Cycle 1 Day 15, study treatment must be taken in the morning due to PK assessments. Once the PK assessments have been completed, patients can determine if they prefer morning or early afternoon dosing, but should maintain a consistent time. Evening doses are strongly not recommended.
- Ribociclib can be administered with or without food.
- Patients should be instructed to swallow the ribociclib 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. Refer to Section 6.2.1.1.4 for use of anti-emetic medications.

[redacted]

- 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.
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pomelos/pummelos, starfruit, Seville oranges or products containing their juice during the entire study. If consumed at baseline, they must be discontinued at least 7 days before the first dose of study treatment (**Note:** Orange juice is allowed).
- 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.
- Goserelin implant should be administered as a subcutaneous injection every 28 days using an aseptic technique under the supervision of a physician. Administration technique should be in accordance with the locally approved label (prescribing information).

6.1.3.2 Additional dosing guidelines for pharmacokinetic sampling/ECG/Chemistry panel collection

On days with PK, ECG sampling, and/or chemistry panel sampling, the following additional guidelines should be followed:

- On a day when PK blood collection is scheduled at the clinic, patients must take study treatment in the clinic under the supervision of the Investigator or designee.
- On a day of chemistry panel sampling, patients must be fasting from all food and drink for at least 8 hours overnight. Water is allowed during all fasting periods; however coffee, tea and juice are not permitted during the fasting period. Patients must also take study treatment in the clinic under the supervision of the Investigator or designee.
- The patient may take the study treatment with or without food; however, dietary habits around the time of dosing should be as consistent as possible on days of PK sampling.
- If a pre-dose ECG measurement should be collected, then the ECG measurement should occur before dosing of the study treatment.
- If a pre-dose PK sample should be obtained, then the sample should be collected after the ECG and before dosing of the study treatment.
- Pre-dose samples should be drawn prior to dosing. The sampling time of the PK samples and the dosing time must be precisely recorded in the eCRF. Furthermore, the dosing date and time the study treatment was taken on the day before the PK assessment must be precisely recorded in the eCRF.
- Post-dose PK samples should be collected after dosing of the study treatment. PK sample collection will be performed according to Section 8.5.1.

6.1.4 Guidelines for continuation of treatment

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

Patients who permanently discontinue the NSAI (letrozole or anastrozole) for any reason must discontinue ribociclib and/or goserelin and move to End-of-Treatment Phase. Patients who permanently discontinue ribociclib for any reason other than disease progression, may continue on a NSAI (and goserelin if premenopausal) within the Treatment Phase per investigator's discretion until disease progression, unacceptable toxicity, death or discontinuation from study

[redacted]

treatment due to any other reason and continue to be followed for safety and/or efficacy. Patients who only discontinue goserelin (e.g. after bilateral oophorectomy), if postmenopausal status is confirmed and with the Sponsor's agreement, may continue on ribociclib and NSAI per investigator's discretion in the Treatment Phase as described above.

6.1.5 Treatment duration

Patients will receive study treatment until disease progression (radiologically documented according to RECIST 1.1 criteria), unacceptable toxicity, death, or discontinuation from the study treatment for any other reason.

6.1.5.1 Treatment beyond disease progression

Continuation of study treatment beyond initial disease progression (RECIST 1.1) will not be allowed.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications (other than study drugs), procedures, and significant non-drug therapies (including vitamins, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be recorded on the eCRFs.

The patient must be told to notify the investigational site about any new medications she takes after the start of the study treatment.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication lists (see Table 16-1 in Section 16.1, these lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions).

Patients taking a concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as much as it is medically feasible and indicated. Any change in the dose or schedule of any concomitant medication throughout the study period should be clearly documented.

6.2.1.1 Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, antiemetics and anti-diarrheals are allowed. Please consult the list of prohibited medications and the list of use with caution medications for further guidance. Potential drug interaction between ribociclib and concomitant medications should always be taken into consideration when prescribing such medications.

6.2.1.1.1 Bisphosphonates and denosumab

Bisphosphonates and denosumab are generally allowed with the following comments:

- Chronic concomitant bisphosphonate/denosumab therapy for the prevention of bone metastasis is not permitted.
- Bisphosphonate/denosumab therapy for the treatment of osteoporosis is permitted.

[redacted]

- Bisphosphonate/denosumab therapy for the prevention of skeletal related events for patients with bone metastases is permitted.

The days of PK blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of PK sampling, if medically feasible.

6.2.1.1.2 Hematopoietic growth factors

Prophylactic use of white blood cell (WBC) growth factors with ribociclib is not recommended.

6.2.1.1.3 Palliative radiotherapy

Palliative radiation is permitted. It should not be delivered to a target lesion. Cumulative courses of radiotherapy should not encompass >25% of irradiated bone marrow. (see Section 16.2).

If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

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

6.2.1.1.4 Use of antiemetic medications

Ribociclib has low to minimal emetogenic potential according to the 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, v3.2018; 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 16.1 for a list of medications that are prohibited or allowed to be used with caution.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during combined ribociclib, NSAI, and goserelin treatment in this study are listed below (see Table 16-2 in Section 16.1, 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 from patient use 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)

[redacted]

- Medications that carry a possible risk for QT prolongation (may precipitate QT prolongation and TdP)
- Sensitive substrates of the renal transporters MATE1/2 and OCT1/2 (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 this transporter, although no animal or clinical data are available to support these statements)

6.2.1.2.1 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 during the study treatment with ribociclib, except for:

- Topical applications (e.g. for 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 (e.g. for chronic obstructive pulmonary disease or as an antiemetic).

6.2.2 Prohibited medications

The following medications are prohibited during study treatment (see Table 16-1 in Section 16.1, 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 from 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 anti-neoplastic therapies.
- Herbal medications/preparations or 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 preparations/medications at least 7 days prior to first dose of study treatment.
- Hormonal contraception, or hormonal medications used as a hormonal replacement therapy for symptoms of menopause, phytoestrogens (as these have potential to reduce efficacy of ET).

It is important to consider potential DDIs when using concomitant medications to treat hot flushes and other anticipated symptoms associated with the use of ET and/or goserelin.

[redacted]

6.2.3 Drug with QT prolongation

As far as possible, avoid co-administering medications with a "Known", "Possible" or "Conditional" risk of TdP or any other medication with the potential to increase the risk of drug-related QT prolongation (e.g. via a potential drug-drug interaction (DDI) increasing the exposure of ribociclib or the exposure of the QT prolonging drug).

If concomitant administration of drugs with a known risk of QT prolongation or TdP is required and cannot be avoided, ribociclib must be interrupted.

If during the course of the study, concomitant administration of a drug with "Possible" or "Conditional" risk of QT prolongation or TdP is required, based on the Investigator's assessment and clinical need, ribociclib 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).

Refer to the ribociclib Investigators Brochure and drug package insert and Section 16.1 for information on possible interactions with other drugs.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

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

6.3.2 Treatment assignment, randomization

At Cycle 1 Day 1 visit, all eligible patients will be randomized via Interactive Response Technology (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. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Patients will be randomized to one of the two treatment arms (Section 3 and Section 6.1). Randomization will be stratified by the presence of lung and/or liver metastasis.

[redacted]

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment assignment will be open to patients, investigator staff, persons performing the assessments, and the clinical trial team (CTT).

6.5 Dose modification

6.5.1 Dose modifications

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. Refer to Table 6-2 for guidance. Ribociclib dose must not be re-escalated once decreased.

Dose reductions are not planned for goserelin, or the NSAIs. For information on goserelin or NSAIs and management of their related adverse events, refer to prescribing information.

Any changes to the dose or interruption of dosing must be recorded on the Dosage Administration Record eCRF.

6.5.1.1 Ribociclib

Patients in Arm 1 can only have one ribociclib dose reduction from 400 mg to 200 mg. Patients in Arm 2 can have two sequential ribociclib dose reductions from 600 mg to 400 mg and then from 400 mg to 200 mg. If a patient on 200 mg has an adverse event that necessitates further dose reduction, the patient must be permanently discontinued from ribociclib.

Table 6-2 Dose modification guidelines

	Arm 1 – Ribociclib 400 mg	
	Dose	**Number of tablets & strength**
Starting dose	**400 mg**	2 x 200 mg tablets
First dose reduction	200 mg	1 x 200 mg tablet
Second dose reduction	Not applicable	Patient must permanently discontinue
	Arm 2 – Ribociclib 600 mg	
Starting dose	**600 mg**	3 x 200 mg tablets
First dose reduction	400 mg	2 x 200 mg tablets
Second dose reduction	200 mg	1 x 200 mg tablet

Recommendations for dose reduction, interruption or discontinuation of ribociclib in the management of study drug related adverse reactions are summarized in Table 6-3, Table 6-4, Table 6-5, Table 6-6. No dose re-escalation is permitted.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. However, for events requiring discontinuation,

[redacted]

treatment must be discontinued. If dosing was interrupted for > 28 days due to ribociclib-related toxicity, ribociclib must be discontinued.

Table 6-3 Ribociclib dose adjustment and management recommendations for hematological adverse reactions (CTCAE v4.03)

Toxicity/Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	
Grade 1(≥75 x 10^9/L)	No dose adjustment required.
Grade 2 (≥50 x 10^9/L – <75 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose.
Grade 3 (≥25 x 10^9/L - <50 x 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 x 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 x 10^9/L)	No dose adjustment required.
Grade 2 (≥1.0 - <1.5 x 10^9/L)	No dose adjustment required.
Grade 3 (≥0.5 - <1.0 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 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 x 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 x 10^9/L)	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate ribociclib at the next lower dose level.
Febrile neutropenia	
Grade ≥3 ANC (<1.0 x 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 x 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 recommendation for hepatic toxicities (CTCAE v4.03)

Grade	Dose Adjustment and Management Recommendations
HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48-72h later)	Maintain dose level with LFTs monitored every two weeks.
Grade 2 (> 1.5 – 3.0 x 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 (one for the 400 mg arm), or recovery to ≤ grade 1 is > 28 days, discontinue ribociclib.
Grade 3 (> 3.0 – 10.0 x 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 x 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 x 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.	
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 x 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 (one for the 400 mg arm) or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib.
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib.

Grade	Dose Adjustment and Management Recommendations
	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 x 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 (one for the 400 mg arm) or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib.
Grade 4 (> 20.0 x 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 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis Or For patients with elevated AST or ALT or total bilirubin at baseline: [AST or ALT >2 x baseline AND >3.0x ULN] OR [AST or ALT 8.0 x ULN]- whichever is lower- **combined with** [total bilirubin > 2 x baseline AND >2.0 x 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 metastases, and alcohol intake.	

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

Grade	Dose Adjustment and Management Recommendations
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. Consider collecting a time matched PK sample; record date and time of last study drug intake.
1* QTcF 450-480 ms	Perform steps 1-4 as directed in “For All Grades” No dose adjustment required.

[redacted]

Grade	Dose Adjustment and Management Recommendations
2* QTcF 481-500 ms	Follow the dose modification guidelines applicable to the corresponding treatment arm:
• **Arm 1 (ribociclib 400mg)**	Interrupt ribociclib. Perform steps 1-4 as directed in “For All Grades.” Perform a repeat ECG within one hour of the first QTcF of ≥ 481 ms. **Repeat ECG as clinically indicated until the QTcF returns to < 481 ms. Reinitiate at the same dose level. No dose adjustment required for first occurrence.** If QTcF ≥ 481 ms recurs (i.e. a second occurrence), ribociclib should be reduced by 1 dose level. If QTcF ≥ 481 ms recurs again (i.e. third occurrence), ribociclib must be permanently discontinued. 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.
• **Arm 2 (ribociclib 600mg)**	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Performed a repeat ECG within one hour of the first QTcF of ≥ 481 ms. **Repeat ECG as clinically indicated until the QTcF returns to < 481 ms and then reinitiate ribociclib reducing 1 dose level.** If QTcF ≥ 481 ms recurs (i.e. a second occurrence), ribociclib should be reduced again by 1 dose level. If QTcF ≥ 481 ms recurs again (i.e. third occurrence), ribociclib must be permanently discontinued. 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	Interrupt ribociclib. Perform steps 1-4 as directed in “For All Grades.” Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. 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. • If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in “For All Grades,” discontinue ribociclib. 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 If QTcF of ≥ 501 ms recurs, discontinue ribociclib.

Grade	Dose Adjustment and Management Recommendations
4* [QT/QTcF ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	Discontinue ribociclib. Perform steps 1-4 as directed in "For All Grades." • Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.

*All values refer to the average of triplicate measurements

Table 6-6 Ribociclib dose adjustment and management recommendation for ILD/pneumonitis (CTCAE v4.03)

Grade	Dose Adjustment and Management Recommendations
1 (asymptomatic)	No dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated.
2 (symptomatic)	Interrupt ribociclib dose until recovery to Grade ≤1, then resume ribociclib at the next lower dose level*.
3 and 4 (severe)	Discontinue ribociclib

* An individualized benefit-risk assessment should be performed before resuming ribociclib

6.5.1.2 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.

Patients who experience renal impairment (suspected to be related to study treatment of grade 2 or higher during the treatment period), should discontinue treatment and should be followed for safety assessments.

For all other adverse events, including Toxic Epidermal Necrolysis (TEN), which is a grade 4 event by CTCAE, please follow recommendations in Table 6-7.

Table 6-7 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.

[redacted]

6.5.2 Follow-up for toxicities

6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases

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

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL values. 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 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: ALP elevation > 2.0 x 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 or hepatocellular liver injury or mixed type injury.

In the absence of cholestasis, patients must be immediately discontinued from study drug treatment, and repeat Liver Function Tests (LFTs) performed 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 consideration of the possibility of progression of liver metastases 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; progressing or new liver metastases and biliary tract disease.

[redacted]

- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, 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.
- Obtaining a PK sample, as close as possible to last dose of study drug.
- Considering a liver biopsy, as clinically indicated to assess pathological change and degree of potential liver injury.

All cases of potential DILI meeting the laboratory criteria defined above, with no other alternative cause explaining the LFT abnormalities identified, should be considered as "medically significant", thus meeting the definition of SAE (Section 10.1.2), 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.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

On days when the patient is administered the study treatment during a visit at the study center, compliance will be assured by the investigator or his/her designee. Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with ribociclib, as detailed in pharmacokinetics section.

6.6.2 Emergency breaking of assigned treatment code

Not applicable as this is an open-label study.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT 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

[redacted]

personnel will detach the outer part of the label from the packaging and affix it to the source document.

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. 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. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the study. 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.

6.7.1.2 Handling of additional treatment

Not applicable.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/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 her understanding. If the patient is capable of doing so, 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.

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.

[redacted]

Information about common side effects already known about the investigational drug can be found in the current ribociclib IB and Kisqali® prescribing information, as appropriate. 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 CBP 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.

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

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

Allowed visit windows are specified as follows (unless otherwise specified):

- Screening assessments must occur within 28 days prior to randomization or within 14 days prior to randomization for selected assessments (note: the 28-day screening period does not apply to the informed consent process).
- There will be no visit window for Cycle 1 Day 1.
- Radiological assessments 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).
- For all other visits, a ± 3 days window is permitted for the applicable assessments, to take into account scheduling issues (applicable assessments should be performed and reviewed prior to dosing).

Table 8-1 Assessment Schedule

Period	Screening		Treatment phase										Post treatment phase
Visit Name	Screening		Cycle 1		Cycle 2	Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycle 7 and every third cycle	End of treatment (within 15 days from the last dose of study treatment)	Safety follow up from the last dose of study treatment + 30 days	Efficacy follow up
Days	-28 to -1	-14 to -1	1	15	1	1	15	1	1	1	1	-	-	-
Informed consent	X (before screening)													
IRT Screening (after ICF)	X													
Disposition	X											X		X
Demographics	X													
Inclusion / Exclusion criteria	X													
Medical History	X													
Diagnosis and extent of cancer	X													
Prior antineoplastic therapies	X													
Concomitant medications	Continuous - up to 30 days after the last dose of study treatment													
Prior or concomitant non-drug therapies/procedures	Continuous - up to 30 days after the last dose of study treatment													
Eligibility checklist (within IRT)	S													
IRT Randomization			X											
IRT study drug dispensation			X		X	X		X	X	X	X			
IRT discontinuation ribociclib												X		
Physical Examination		S	S		S	S		S			S	S		
ECOG performance status		X	X		X	X		X			X	X		
Vital Signs		X	X		X	X		X	X	X	X	X		

[redacted]

Period	**Screening**		**Treatment phase**										**Post treatment phase**
Visit Name	**Screening**		**Cycle 1**		**Cycle 2**	**Cycle 3**		**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7 and every third cycle**	**End of treatment (within 15 days from the last dose of study treatment)**	**Safety follow up from the last dose of study treatment + 30 days**	**Efficacy follow up**
Days	**-28 to -1**	**-14 to -1**	**1**	**15**	**1**	**1**	**15**	**1**	**1**	**1**	**1**	**-**	**-**	**-**
Body Weight		X						X			X	X		
Body Height		X												
Hematology		X	X	X	X	X		X	X	X	X	X		
Chemistry		X	X	X	X	X		X	X	X	X	X		
Coagulation		X	As clinically indicated											
Serum pregnancy test (women CBP)		S										S		
Urine pregnancy test (women CBP)			S		S	S		S	S	S	S		S	
Tumor assessment	X		Every 8 weeks during the first 18 months, every 12 weeks until 36 months, and thereafter as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision and EOT[1] (±7 days for all intervals)											
Body fluid / tissue collection / results	As clinically indicated until disease progression													
Whole body bone scan	X (within 42 days prior to randomization)		As clinically indicated											
Adverse Events	Continuous – up to 30 days after last dose of study treatment													

[redacted]

Period	Screening		Treatment phase										Post treatment phase
Visit Name	**Screening**		**Cycle 1**		**Cycle 2**	**Cycle 3**		**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7 and every third cycle**	**End of treatment (within 15 days from the last dose of study treatment)**	**Safety follow up from the last dose of study treatment + 30 days**	**Efficacy follow up**
Days	**-28 to -1**	**-14 to -1**	**1**	**15**	**1**	**1**	**15**	**1**	**1**	**1**	**1**	**-**	**-**	**-**
Electrocardiogram (ECG)[2]		X[3]	X	X	X	X	X	X	X	X	X (only for patients with average QTcF ≥ 481 ms any time point prior to cycle 7, then assessed Day 1 of every cycle)	X		
PK blood collection				X										
Ribociclib			Days 1-21 of every cycle											
NSAI			Daily											
Goserelin (if applicable)			Day 1 of every cycle											
Antineoplastic therapies since discontinuation of study treatment												X	X	X

[redacted]

Period	Screening		Treatment phase										Post treatment phase
Visit Name	Screening		Cycle 1		Cycle 2	Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycle 7 and every third cycle	End of treatment (within 15 days from the last dose of study treatment)	Safety follow up from the last dose of study treatment + 30 days	Efficacy follow up
Days	-28 to -1	-14 to -1	1	15	1	1	15	1	1	1	1	-	-	-

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] For patients with documented disease progression (either during the treatment phase or post treatment phase), an additional efficacy assessment should be performed according to the regularly scheduled interval (every 8 weeks during the first 18 months and every 12 weeks until 36 months) but not later than 12 weeks from the efficacy assessment at which progressive disease was determined (±7 days for all intervals).
[2] Triplicate recording, standard 12-lead.
[3] Screening ECG should be performed or repeated after any electrolyte abnormalities are corrected as per the inclusion criteria.

[redacted]

8.1 Screening

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

Re-screening of patients is only allowed once per patient if the patient was not registered as entering the treatment phase before (i.e. IRT randomization). In this case a new subject number will be generated, and a specific rescreen form will be added in eCRF, to collect the original subject number. This data will be used to link the two subjects for reporting and validation.

For laboratory and ECG evaluations used to determine eligibility, a 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. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria. A new informed consent must be signed if the investigator chooses to re-screen the patient following a screen failure.

If a new informed consent form is signed, adverse events and medical history will be assessed relative to the new informed consent date.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to randomization (including before signing the main study ICF) can be considered 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 but fail to be started on treatment for any reason, will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic information, 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 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.

8.2 Subject demographics/other baseline characteristics

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

- Demography (age, sex, race, ethnicity)
- Diagnosis and extent of cancer (including staging at initial diagnosis and histology/cytology)

[redacted]

- 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.
- Menopausal status
- ER, PgR and HER2 status
- All prior antineoplastic therapies including anticancer surgical interventions, radiation therapies, and/or systemic treatments 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 Concomitant medications eCRF page or concomitant non-drug therapies/procedures eCRF page and updated on a continuous basis if there are any new changes to the medications.

Furthermore, the following assessments will be performed:

- Vital signs
- Height and weight
- Physical examination
- Performance status (ECOG)
- Laboratory evaluations (hematology, chemistry, coagulation, serum pregnancy test for women of CBP)
- ECG
- Radiological assessments (e.g. CT Scan)

8.3 Efficacy

8.3.1 Imaging tumor assessments

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.2 (Section 16.2) based on RECIST Version 1.1 (Eisenhauer et al 2009). The local investigator's assessment will be used for treatment decision making and determination of progressive disease. The imaging assessment collection plan is presented in Table 8-2.

Imaging data for all patients will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The central review of the scans will be carried out in a blinded fashion for all patients. Details regarding blinded independent review committee (BIRC) assessment will be provided in the BIRC charter. Please refer to the site imaging operations manual for additional information on the image acquisition and data collection by the imaging CRO.

Information regarding prior interventions (e.g. radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO via the Baseline Clinical Form along with the baseline images for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

[redacted]

Information regarding cytology results should be transmitted to the imaging CRO via the Cytology Form for all visits, when applicable, for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

Physical exam tumor assessments, photography, pathology and histology/cytology results, as well as, information regarding prior interventions, pre-existing radiographic findings that mimic metastatic disease at baseline/screening and on-study interventions may be transmitted to the imaging CRO as part of the BIRC review.

Patients should have at least one documented measurable lesion (per RECIST 1.1).

Imaging assessments will be performed at screening within 28 days prior to randomization and subsequently every 8 weeks following randomization during the first 18 months and every 12 weeks until 36 months, then as clinically indicated. Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to randomization (and within 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. The 8-week and 12 week indicated intervals should be respected regardless of whether study treatment is temporarily withheld. Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for objective response are first met. In the case that tumor assessment is performed <8 weeks from the first assessment of an objective response to confirm PR/CR, subsequent tumor assessments should revert back to the protocol schedule outlined in Table 8-1 . See Table 8-2 for details of assessments.

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.

For all patients with radiological documentation of progression of disease (either during the treatment phase or post treatment phase), for confirmatory purposes an additional efficacy assessment should be performed according to the regularly scheduled interval (every 8 weeks during the first 18 months and every 12 weeks until 36 months) but not later than 12 weeks from the efficacy assessment at which progressive disease was determined.

If a patient discontinues treatment for reasons other than radiological documentation of progression of disease, an efficacy assessment should be performed at the time of EOT unless a CT/MRI for tumor measurement was performed within 21 days from EOT visit. Efficacy assessments should continue according to the scheduled visit per Table 8-1 and Table 8-2.

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 and Table 8-2. 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 study, 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, fluoro-deoxyglucose positron emission tomography (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 baseline. These should be followed throughout the study according to the schedule outlined in Table 8-2.

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. 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 (Section 16.2). 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.

Results from tissue or body fluid collection should be recorded in the eCRF to complement radiographic findings.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

[redacted]

Table 8-2 Imaging collection plan

Procedure	Screening: Day -28 to Day -1	Treatment Phase[1]	End of Treatment[1,2]	Post-Treatment Phase[2]
CT or MRI with contrast (Chest, Abdomen, Pelvis)	Mandated	Every 8 weeks during the first 18 months, then every 12 weeks until 36 months and thereafter as clinically indicated (± 7 days for all intervals)	Mandated.	Every 8 weeks during the first 18 months, every 12 weeks until 36 months, and thereafter as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision (± 7 days for all intervals). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
Brain CT or MRI	Mandated at screening if history of, existing or suspected brain metastases	If brain lesion at screening: every 8 weeks during the first 18 months, then every 12 weeks until 36 months and thereafter as clinically indicated (± 7 days for all intervals)	Mandated only if brain lesion at screening.	If brain lesion at screening: Every 8 weeks during the first 18 months. then every 12 weeks until 36 months and thereafter as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision (± 7 days for all intervals). In the absence of disease

[redacted]

Procedure	Screening: Day -28 to Day -1	Treatment Phase[1]	End of Treatment[1,2]	Post-Treatment Phase[2]
				progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
Whole body bone scan[3]	Mandated (Day -42 to Day -1)	As clinically indicated		
Bone X-ray, CT or MRI	Only if skeletal abnormalities identified by whole body bone scan[3] at screening, which are not visible in the chest, abdomen, pelvis CT/MRI.	If bone lesion at screening, every 8 weeks during the first 18 months, then every 12 weeks until 36 months and thereafter as clinically indicated (± 7 days for all intervals)	Mandated only if bone lesion at screening.	If bone lesion at screening, every 8 weeks during the first 18 months, then every 12 weeks until 36 months and thereafter as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision (± 7 days for all intervals). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
Skin color Photography	Only if skin lesions at screening	If skin lesions at screening, every 8 weeks during the first 18 months, then every 12 weeks until 36 months	Mandated if skin lesions at screening.	If skin lesions at screening, every 8 weeks during the first 18 months, then every 12 weeks until 36 months

[redacted]

Procedure	Screening: Day -28 to Day -1	Treatment Phase[1]	End of Treatment[1,2]	Post-Treatment Phase[2]
		and thereafter as clinically indicated (± 7 days for all intervals)		and thereafter as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision (± 7 days for all intervals). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
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 8 weeks during the first 18 months, then every 12 weeks until 36 months and thereafter as clinically indicated (± 7 days for all intervals)	Mandated if lesion at screening.	If lesion identified at screening, every 8 weeks during the first 18 months, then every 12 weeks until 36 months and thereafter as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision (± 7 days for all intervals). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease

[redacted]

Procedure	Screening: Day -28 to Day -1	Treatment Phase[1]	End of Treatment[1,2]	Post-Treatment Phase[2]
				progression, only in this case a ±14 days window is allowed.

[1]Tumor evaluation at End of treatment (EOT) is required for patients who discontinue study treatment before the first scheduled post-baseline tumor assessment (week 8) and for patients whose previous tumor assessment did not demonstrate progressive disease (PD) and was done more than 21 days prior to end of treatment visit.

[2]For patients with documented disease progression (either during the treatment phase or post treatment phase), an additional efficacy assessment should be performed according to the regularly scheduled interval (every 8 weeks during the first 18 months and every 12 weeks until 36 months) but not later than 12 weeks from the efficacy assessment at which progressive disease was determined (±7 days for all intervals).

[3]Whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, NaF PET or FDG-PET.)

8.3.2 Appropriateness of efficacy assessments

The measurements are standard based on the New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). (Eisenhauer et al 2009).

8.4 Safety and tolerability

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-3 Assessments & Specifications

Assessment	Specification
Physical examination	The 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. 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 eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure, pulse measurement, and body temperature. Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for five minutes.
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 as specified in Table 8-1.

ECOG Performance status scale will be used as described in Table 8-4.

[redacted]

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

8.4.1 Laboratory evaluations

Clinical laboratory analyses (Hematology, Chemistry, Coagulation) are performed by the central laboratory according to the Assessment schedule outlined in Table 8-1. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Visit windows of +/- 3 days are allowed for all visits except at Cycle 1 Day 1.

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.

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used with the exception of FSH and plasma estradiol levels to determine menopausal status and pregnancy testing, if applicable. eGFR will be done using the 4-variable MDRD formula: eGFR in mL/min per 1.73 m^2 = 175 x $SerumCr^{-1.154}$ in mg/dL x $age^{-0.203}$ x 1.212 (if patient is black) x 0.742 (female).

Unscheduled local laboratory assessments may be performed if medically indicated to document an adverse event (potential) or when the treating physician cannot wait for central laboratory results for decision making (e.g. dose modifications). In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the eCRF if they are used for treatment decisions and any the following criteria are met:

- There are no concomitant central results available, or
- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event where the severity is worse than the one reported by the central lab

At any time during the study, abnormal laboratory parameters which are clinically relevant 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 AE eCRF page. Laboratory data will be summarized using the CTCAE version 4.03. Additional analyses are left to the discretion of the investigator.

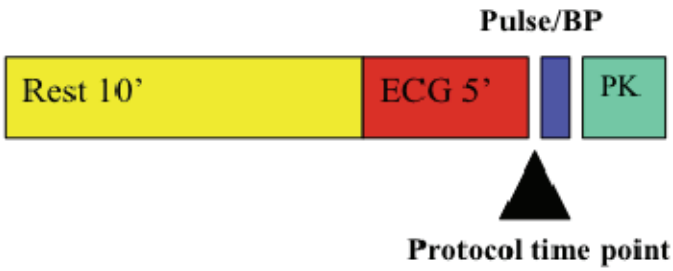
Table 8-5 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, %s are acceptable))
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Total Calcium (corrected for albumin), Magnesium, Phosphorus, Sodium, Potassium, Creatine Kinase, Creatinine, Direct Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT), Prothrombin time (PT)
Pregnancy Test	Serum and Urine pregnancy test FSH and estradiol for confirmation of menopausal status (pre/post) Note: FSH and estradiol are not recorded in eCRF, but used to determine menopausal status, if needed

8.4.2 Electrocardiogram (ECG)

Standard triplicate 12 lead ECG assessments will be performed after the patient has been resting for 5-10 min prior to each time point indicated in Table 8-6 below. Triplicate ECGs should be taken approximately 2 minutes apart. The combined QTcF values from these triplicate ECGs will be averaged to provide a single value for each time point.

Timing of study procedures (* *if applicable):*



*ECG assessments are to be done prior PK sampling (if applicable).

Table 8-6 Central ECG collection plan

Cycle	Patients	Day	Time	ECG Type
Screening	All	-14 to -1	Anytime	Triplicate 12 Lead
1	All	Day 1	Pre-dose[1]	Triplicate 12 Lead
			2h post-dose (± 15 min)	Triplicate 12 Lead
			4 h post-dose (± 15 min)	Triplicate 12 Lead
	All	Day 15[2]	Pre-dose[1]	Triplicate 12 Lead
			2h post-dose (± 15 min)	Triplicate 12 Lead
			4 h post-dose (± 15 min)	Triplicate 12 Lead
2	All	Day 1	Pre-dose[1]	Triplicate 12 Lead
3	All	Day 1	Pre-dose[1]	Triplicate 12 Lead
			2h post-dose (± 15 min)	Triplicate 12 Lead
		Day 15	Pre-dose[1]	Triplicate 12 Lead
			2h post-dose (± 15 min)	Triplicate 12 Lead
4	All	Day 1	Pre-dose[1]	Triplicate 12 Lead
5	All	Day 1	Pre-dose[1]	Triplicate 12 Lead
6	All	Day 1	Pre-dose[1]	Triplicate 12 Lead
			2h post-dose (± 15 min)	Triplicate 12 Lead
All other cycles[3]	Patients with average QTcF ≥ 481 ms at any time point prior to cycle 7	Day 1	Pre-dose[1] (At every cycle)	Triplicate 12 Lead
			2h post-dose (± 15 min) [starting at cycle 10 and every 3rd cycle only[3]]	Triplicate 12 Lead
EOT			Anytime	Triplicate12 Lead
Unscheduled ECG			Anytime[1]	Triplicate 12 Lead

[1]The exact date and time of dosing must be recorded on the appropriate eCRF

[2]ECG assessments are to be done **prior** to PK sampling

[3] Pre-dose ECG on the first day of every cycle. Additionally, 2 h post-dose in every 3rd cycle (i.e. Cycle 10, 13, 16, 19, etc.)

Note:

In order to ensure ECG evaluation is received by the central laboratory for eligibility assessment, it is advisable to perform the ECG at least 72 hours prior the scheduled randomization date.

If a QTcF value of ≥ 481 ms is obtained (as the average of a triplicate) at any time after randomization, study treatment must be interrupted, repeat ECG(s) and follow management guidelines detailed in Table 6-5.

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 in triplicate. Local cardiologist ECG assessment may be performed at any time during the study at the discretion of the investigator.

All ECGs including unscheduled triplicate ECGs with clinically relevant findings, collected during the study should be transmitted to a central laboratory and will be centrally reviewed by

[redacted]

an independent reviewer. The results of the centrally assessed ECGs are automatically transferred into the clinical database.

The results of the local ECGs will be recorded in the eCRF if they are used for treatment decisions and any of the following criteria are met:

- There are no concomitant central results available, or
- Local ECG results document an adverse event not reported by the central lab, or
- Local ECG results document an adverse event where the severity is worse than the one reported by the central lab

Any original ECG not transmitted to a central laboratory should be forwarded for central review. 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 eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

In the event that a QTcF value of > 500 ms is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the time and date of the last study drug intake to determine the drug exposure.

8.4.3 Pregnancy and assessments of fertility

When applicable, FSH, estradiol, serum and urine pregnancy tests are to be performed locally according to Table 8-1 and Table 8-5.

At screening and EOT visit, a serum pregnancy test should be performed for women of CBP. During the treatment phase and at safety follow-up visit, a urine pregnancy test is sufficient.

If applicable, FSH and estradiol will be done at screening for clarification of CBP and confirmation of menopausal status (see Section 5.1, Criteria 13 and 14).

8.5 Additional assessments

8.5.1 Pharmacokinetics

Blood samples will be collected from all study patients for the analysis of plasma concentrations of ribociclib and assessment of ribociclib pharmacokinetics. In a subset of patients (~20 patients per arm), extensive PK blood sampling will be performed to provide approximately 12 evaluable patients to characterize PK per arm and samples will be collected as specified in Section 8.5.1.1.1. In all the remaining patients, PK samples will be collected matching the ECG measurement time points as specified in Table 8-8.

An unscheduled PK blood sample may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the investigator's discretion. If a patient discontinues from the study treatment due to toxicities related to study treatment, an unscheduled PK blood sample may be obtained as soon as possible after the last dose and the date and time of last dose recorded. In addition, an unscheduled blood sample may be collected if additional ECG measurements are conducted.

[redacted]

The date and exact time of dosing as well as the date and actual time of blood sampling for PK collection (including both scheduled and unscheduled PK samples) must be recorded on the appropriate eCRF pages. In addition, the exact time of dosing on the previous day must be precisely recorded.

Any sampling problems (e.g., subject refused, technical collection issue, physician decision or other issue) have to be recorded on the eCRF.

If vomiting occurs, the date and exact time of vomiting should be recorded if it occurs within 4 hours of dosing on the day before or the day of PK sampling.

PK parameters, such as Cmax, Tmax, and AUC0-24h, will be estimated (when feasible) from individual plasma concentration-time profiles using appropriate methods and software; a detailed description of the planned analyses is given in Section 12.5.4.

8.5.1.1 Pharmacokinetic blood collection and handling

For detailed instructions for the collection, handling, and shipment of PK samples, please refer to the PK laboratory manual.

8.5.1.1.1 PK blood collection

Blood collections for PK assessment of ribociclib will be obtained according to Table 8-7 and Table 8-8. The exact clock time of dosing, as well as actual sample collection date and time will be entered on the PK blood collection summary page and dosage administration page of the eCRF. Sampling problems will be noted in the relevant field of the eCRF.

Table 8-7 Schedule of extensive pharmacokinetic blood collection

Cycle	Day	Scheduled Time Point Relative to Dosing	Dose Reference ID for ribociclib		PK Sample No. for ribociclib	Blood Volume (mL)
1	15	Pre-dose (0 h)[a]	111	11[b]	101	2
1	15	2 h post-dose (± 15 min)	111		102	2
1	15	4 h post-dose (± 30 min)	111		103	2
1	15	6 h post-dose (± 30 min)	111		104	2
1	15	24 h post-dose (± 2 h)[a]	111		105	2
NA	NA	Unscheduled: PK samples related to a QTcF > 500 msec[c]	NA		1001+[c]	2
NA	NA	Unscheduled: Anytime[d]	NA		2001+[d]	2

NOTE: One single blood draw will be obtained from each patient at each time point. Sampling time is relevant to ribociclib dose.

[a] Collect PK sample approximately 24 h (± 2 h) after last dose and immediately before drug administration.

[b] Dose reference ID to collect last dose.

[redacted]

Cycle	Day	Scheduled Time Point Relative to Dosing	Dose Reference ID for ribociclib	PK Sample No. for ribociclib	Blood Volume (mL)
[c] Unscheduled PK samples related to a prolonged QT will be uniquely, sequentially numbered 1001, 1002, 1003, etc. [d] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely, sequentially numbered 2001, 2002, 2003, etc.					

Table 8-8 Schedule of non-extensive pharmacokinetic blood collection

Cycle	Day	Scheduled Time Point Relative to Dosing	Dose Reference ID for ribociclib		PK Sample No. for ribociclib	Blood Volume (mL)
1	15	Pre-dose (0 h)[a]	222	22 [b]	201	2
1	15	2 h post-dose (± 15 min)	222		202	2
1	15	4 h post-dose (± 30 min)	222		203	2
NA	NA	Unscheduled: PK samples related to a QTcF > 500 msec[c]	NA		3001+[c]	2
NA	NA	Unscheduled: Anytime[d]	NA		4001+[d]	2
NOTE: One single blood draw will be obtained from each patient at each time point. Sampling time is relevant to ribociclib dose. [a] Collect PK sample approximately 24 h (± 2 h) after last dose and immediately before drug administration. [b] Dose reference ID to collect last dose. [c] Unscheduled PK samples related to a prolonged QT will be uniquely, sequentially numbered 3001, 3002, 3003, etc. [d] Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely, sequentially numbered 4001, 4002, 4003, etc.						

8.5.1.2 Analytical method

The concentrations of ribociclib will be measured in human plasma using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of approximately 1.0 ng/mL for ribociclib.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when all study treatment components (ribociclib, NSAI, and goserelin, if applicable) are permanently stopped.

[redacted]

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:

- Patient/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Adjustments to study treatment due to toxicity that result in discontinuation as per recommendations in the dose modifications sections
- Any situation in which study participation might result in a safety risk to the patient
- Progressive disease

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 'Withdrawal 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, 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.

Patients who discontinue study treatment (i.e. ribociclib +NSAI, and goserelin, if applicable), should undergo 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 the Assessment Schedule. If the decision to discontinue the patient occurs at a regularly scheduled visit, that visit may serve as the EOT visit rather than having the patient return for an additional visit.

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 evaluation of adverse events occuring during the 30 days (±3 days) following the last dose of study treatment.

The investigator must also contact the IRT to register the patient’s discontinuation from study treatment within 2 days of the EOT visit.

9.1.2 Safety evaluations follow-up

All patients will be followed up for safety for at least 30 days (±3 days) after last dose of study treatment. Patients whose treatment is permanently discontinued due to an adverse event, 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. Data collected should be added to the Adverse Events eCRF and the Concomitant Medications eCRF.

[redacted]

9.1.3 Efficacy follow-up

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 8 weeks after randomization during the first 18 months and every 12 weeks until 36 months, then as clinically indicated until disease progression, death, lost to follow-up, or withdrawal of consent. If a patient starts a new anti-cancer therapy prior to progression, tumor evaluations should continue as per the Assessment Schedule until disease progression is documented. In addition, all new anticancer therapies given after the last dose of the study treatment, until disease progression, death, lost to follow-up, or withdrawal of consent (whichever comes first) will be recorded in the eCRFs.

9.1.4 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 allow further collection of personal data

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 keep and use collected study information (including any data resulting from the analysis of a patient's samples until the time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.5 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

[redacted]

calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed.

9.1.6 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 early termination be necessary, patients must be seen as soon as possible and treated as a prematurely 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 study.

9.2 Study completion and post-study treatment

Study completion for a patient occurs when the patient completes the safety and efficacy follow-up periods (as applicable) and any repeat assessments associated with these visits have been documented and followed-up appropriately by the Investigator. In the event of an early study termination decision, the date of that decision must be documented.

All randomized and/or treated patients should have a safety follow-up visit conducted at 30 days (±3 days) after last administration of study treatment (ribociclib, NSAI, and goserelin, if applicable). 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 be conducted when all patients have been treated for at least 6 months from randomization or have discontinued study treatment. The primary analysis data will be summarized in the primary clinical study report (CSR).

Following the cut-off date for the primary analysis reported in the primary CSR, the study will remain open. All additional data for patients that continue to receive study treatment past the data cut-off date for the primary analysis, as allowed by the study protocol, will be reported in the final CSR at the end of the study.

End of study will be declared as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study or have been followed up for approximately 3 years from randomization.
- Patients who in the opinion of the investigator are still deriving clinical benefit in this study can continue provision of study treatment through an alternative setting.
- Another clinical study becomes available that can continue to provide ribociclib in this patient population and all patients ongoing are eligible to be transferred to that clinical study.

Post-study antineoplastic treatment will be at the investigator's discretion.

[redacted]

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 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. Serious adverse events (SAEs) are defined in Section 10.1.2.

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 study 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 10.1.2):

1. Adverse events will be assessed and graded according to the CTCAE version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death corresponding to Grades 1 - 5, will be used. Information about deaths will also be collected through a Death eCRF.
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 lack of efficacy or progression of underlying illness are i) not caused by the study drug, ii) they happen in spite of its administration and/or iii) 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 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken with study treatment.

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

   - Dose not changed
   - Dose reduced
   - Drug interrupted/withdrawn

[redacted]

6. Its outcome (i.e. recovery status or whether it was fatal).

If the event worsens, it should be reported a second time in the eCRF 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 eCRF 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 the 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 at least 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 study treatment, 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 1.1), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (i.e. 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

10.1.2 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:

- Is fatal.
- Is life-threatening (i.e. the adverse event, in the view of the investigator, places the patient at immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

[redacted]

Note that hospitalizations for the following reasons should not be reported as SAEs:

- 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.
- Treatments occurring on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above.

All cases of confirmed of DILI (see Section 6.5.2.1) must be reported as SAE regardless of the severity.

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 (please refer to the ICH-E2D Guidelines).

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 of whether a clinical event has occurred.

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 following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence.

Screen Failures:

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

[redacted]

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.

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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continued, if and how it was treated, and whether the patient continued or withdrew from study participation.

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 Novartis Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) 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 ECs in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

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 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 Drug Exposure in Pregnancy Form and reported by the investigator to the Novartis 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 for any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

[redacted]

10.1.5 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 eCRF irrespective of whether or not they are associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse information 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 eCRF (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

Refer to Section 6.5.2.1 for follow up on potential DILI cases.

10.2.1 Steering Committee

A Steering Committee (SC) will be established and it will be comprised of investigators and Novartis personnel participating in the trial. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will be consulted for protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in the SC charter.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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

[redacted]

be given access to the electronic data capture (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 (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.

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

11.2 Database management and quality control

Novartis personnel (or designated contract research organization (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 World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) 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 all study treatment (s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (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.

Blood samples for laboratory data and PK assessments will be collected by sites and sent to the Novartis designated central laboratory for processing. The laboratory results will be sent electronically to Novartis (or a designated CRO).

Imaging data will be collected at the sites and the data will be transmitted to a designated CRO (if any) for centralized analysis, as well as further processing. Note: Once the radiology review from the blinded independent review committee has been completed, patients' radiological and photography data images should no longer be transmitted to the imaging CRO. Novartis will notify all sites when central imaging submission for the trial is complete.

ECG data will be collected via 12-lead digital ECG machines. The data will be transmitted to Novartis and a designated CRO for centralized cardiac safety analysis, as well as further processing and data reconciliation.

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. Any changes to the database after that time can only be made after written agreement by Novartis development management.

[redacted]

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or 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 GCP, 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 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 study 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 eCRFs 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 eCRFs 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

The primary efficacy and safety analyses will be performed after all patients have been treated for at least 6 months or have discontinued study treatment. Any additional data for patients continuing to receive study treatment past this time and for patients continuing for efficacy follow up (PFS), as allowed by the protocol, will be further summarized in a final study report at the end of the study.

It is planned that the data from all centers participating in the study 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 the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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

[redacted]

FAS will be the default analysis set for all efficacy analysis except the primary endpoint.

The Per-Protocol Set (PPS) is a subset of patients of the Full Analysis Set without major protocol deviations. The PPS will be used for the analysis of the primary efficacy endpoint.

Patients with any of the following protocol deviations may be excluded from the PPS:

- Written informed consent not obtained;
- Patient without HR-positive and HER2-negative advanced breast cancer at baseline;
- Patient received prior CDK4/6 inhibitor;
- Patient without measurable disease at baseline;
- Patient received any prior hormonal anti-cancer therapy for advanced breast cancer, except for ≤ 14 days of a NSAI and/or ≤ 28 days of goserelin prior to randomization for pre-menopausal patients;
- Patient received chemotherapy for advanced breast cancer;
- Patient received different treatment throughout the study than the one randomized to
- Patient had dose reduction of ribociclib within cycle 1

All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the data handling plan and the statistical analysis plan (SAP).

The Safety Set 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/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The Pharmacokinetic Analysis Set (PAS) consists of all patients who received at least one dose of study medication defined as ribociclib and provide at least one evaluable PK concentration.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics/prognostic data will be listed and summarized descriptively by treatment group for the FAS. The summary will also be produced for PPS if the FAS and PPS differ.

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

Relevant medical history and current medical conditions at baseline will be summarized separately 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, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to ribociclib,NSAI and goserelin, as well as dose intensity (computed as the ratio of actual dose received to actual duration) and the relative dose intensity (computed

[redacted]

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 ribociclib, NSAI and goserelin for each patient will be summarized using descriptive statistics (e.g. mean, median, and mode).

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

The number 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(s)

The primary objective in the study is to determine whether the dosing regimen of ribociclib 400 mg QD 3 week-on/1 week-off in combination with NSAI (Arm 1) is non-inferior to the currently approved regimen of 600 mg QD 3 week-on/1 week-off in combination with NSAI (Arm 2) in terms of ORRs assessed by local investigators. As such, the primary efficacy endpoint of the study is to evaluate the non-inferiority of Arm 1 compared to Arm 2, based on the ratio of ORR between the two arms. The experimental arm (Arm 1) will be considered to be non-inferior to the control arm (Arm 2) if the lower 90% CI limit of the ratio of the ORR in Arm 1 to Arm 2 is greater than 0.814. The non-inferiority (NI) margin of 0.814 was chosen to demonstrate the retention of at least 50% of the active treatment effect in terms of ORR for ribociclib in combination with NSAI vs. NSAI alone.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is overall response rate (ORR), defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) assessed by local investigators according to RECIST 1.1 (See Section 16.2 for further details for RECIST 1.1). ORR is based on the tumor evaluations from patients who have been treated for at least 6 months or have discontinued treatment.

12.4.2 Statistical model, hypothesis, and method of analysis

The following statistical hypotheses will be tested to address the primary objective based on the non-inferiority decision rule:

H_{01}: $\theta_1 <= 0.814$ vs. H_{A1} : $\theta_1 > 0.814$

where θ_1 is the ratio of ORR in Arm 1 to ORR in Arm 2. The non-inferiority of Arm 1 to Arm 2 will be established if the lower 90% CI limit of θ_1 is greater than the pre-specified NI margin 0.814.

The primary efficacy variable, ORR, will be based on the PPS population according to the randomized treatment group. The CI of ORR ratio will be constructed using Mantel-Haenszel method to include lung/liver metastasis as the stratification factor.

[redacted]

12.4.3 Handling of missing values/censoring/discontinuations

In the primary analysis, all the eligible overall responses will be considered for the evaluation of best overall response. Only patients with confirmed best overall response as CR or PR will be considered as responders for ORR calculation, and all other patients will be considered as non-responders including patients with best overall response (BOR) as unknown or missing.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

As a sensitivity analysis, the primary analysis for ORR will be repeated in the FAS.

Supportive analyses

As a supportive analysis, the primary analysis will be repeated using Blinded Independent Review Committee (BIRC) assessment.

Proportions of patients with ORR will be presented by treatment group along with approximate 95% confidence intervals. The analysis will be conducted in both PPS and FAS, and the analysis will be conducted using the assessment from local investigators as well as BIRC.

Subgroup analyses to assess the homogeneity of treatment effect based on demographic and baseline disease characteristics may be performed; details about the subgroups to be included will be provided in the study SAP. The analysis will be conducted in both PPS and FAS.

12.5 Analysis of secondary endpoints

12.5.1 Key secondary objective

ECG data will be collected via 12-lead digital ECG machines. The data will be transmitted to a designated CRO for centralized cardiac safety analysis.

The key secondary objective of the study is to evaluate the QTc (with Fridericia's correction) profile of the experimental arm. The objective of mitigating QT prolongation will be met if the upper 90% CI limit of the Δ QTcF at Cycle 1 Day 15 (2 h post-dose) compared to baseline (Cycle 1 Day 1 pre-dose) is less than 20 ms (FDA 2015).This analysis will be based on all patients in the Safety Set that have a non-missing QT assessment performed at baseline and Cycle 1 Day 15 (2h post-dose).

Change from baseline of QTcF at other time points will also be summarized. Notable elevations of QTcF will be summarized based on all on-treatment ECG assessments. The totality of the safety data obtained in Arms 1 and 2, generated from each time point as outlined in the ECG monitoring and assessment schedule, will be compared as part of the overall assessment for QT prolongation risk mitigation.

The last available ECG assessment before the start of study treatment will be used as the ‘baseline’ assessment. Assessments specified to be collected post-dose on the first date of treatment are not considered as baseline values.

In addition to QTcF, other ECG related endpoints will be summarized including PR, QRS, QT, and RR intervals. The summary includes:

[redacted]

1. 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.
2. Shift table baseline to worst on-treatment result for overall assessments
3. Table with descriptive statistics at baseline, post-baseline time points and change from baseline to post-baseline time points.

All ECG data will also be listed by treatment group, patient and visit/time; abnormalities will be flagged.

12.5.2 Efficacy and/or Pharmacodynamic endpoint(s)

Progression free survival (PFS) is defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. PFS will be censored if no PFS event is observed. The censoring date will be the date of the last adequate tumor assessment (see Section 16.2 for further details). Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. PFS will be assessed via a local radiology assessment as well as BIRC according to RECIST 1.1.

PFS will be analyzed in the FAS population according to the randomized treatment group. The PFS 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.

Clinical benefit rate (CBR) is defined as the proportion of patients with a best overall response of complete response (CR), or partial response (PR), or an overall response of stable disease (SD), lasting for at least 24 weeks. CR, PR, and SD are defined as per local review as well as BIRC according to RECIST 1.1 (see Section 16.2 for details).

CBR will be calculated based on the FAS. CBR and its 95% confidence interval will be presented by treatment group.

Time to response (TTR) is defined as the time from the date of randomization to the first documented response of either complete response (CR) or partial response (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 Section 16.2 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.

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to RECIST 1.1 based on tumor response data per local review. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Patients continuing without progression or death due to underlying cancer will be censored at the date

[redacted]

of their last adequate tumor assessment. DOR will be listed and summarized by treatment group for all patients in the FAS with confirmed BOR of CR or PR (see Section 16.2 for details).

12.5.3 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 deaths, including on treatment and post treatment deaths will be provided.

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:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study treatment.
2. On-treatment period: from day of first dose of study treatment to 30 days after last dose of study treatment.
3. Post-treatment period: starting at day 31 after last dose of study treatment.

Adverse events

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged. All information obtained on adverse events will be displayed by treatment group and patient.

The number (and percentage) of patients with treatment emergent adverse events will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

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

Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

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

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

[redacted]

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

All AEs, deaths, and serious adverse events (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.

AESI will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). AESI will be defined at project level and may be regularly updated. The grouping of AEs in AESI according to project standards will be specified in the Case-Retrieval Sheet (CRS) and/or the study statistical analysis plan.

For each specified AESI, number and percentage of patients with at least one event part of the AESI will be reported by treatment group

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) 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 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

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

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03:

- 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 v4.03 grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by CTCAE v4.03:

[redacted]

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other exploratory analyses, for example, figures plotting time course of raw values or change in laboratory tests over time or box plots might be specified in the analysis plan.

12.5.4 Pharmacokinetics

Ribociclib plasma concentration data (and any relevant metabolites such as LEQ803) will be listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point.

Summary statistics will include mean (arithmetic and geometric), SD (standard deviation), CV (arithmetic and geometric), median, minimum, and maximum. The geometric mean and arithmetic mean (SD) plots will also be graphically presented for concentration-time data (concentration time profiles).

Plasma samples will be assayed for LEE011 concentrations by Novartis or Novartis designated laboratory using validated LC-MS/MS methods with a LLOQ of approximately 1.00 ng/mL for ribociclib. All concentrations below the LLOQ will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV.

In approximately 20 patients per arm, extensive PK sampling for ribociclib will be performed as detailed in Section 8.5.1.

For these patients, PK parameters (if available) of ribociclib (and any relevant metabolites), including but not limited to those listed in Table 12-1, will be calculated from the individual concentration-time profile. Pharmacokinetic parameters will be listed by treatment and patient. Any missing PK parameter data will not to be imputed. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

PAS will be used in all pharmacokinetic data analysis and PK summary statistics.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUC0-24	The AUC from time zero to 24 hours (ng*h/mL)
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (ng*h/mL)
AUCinf	The AUC from time zero to infinity (ng*h/mL)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng/mL)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (h).
CL/F	The total body clearance of drug from the plasma (L/h)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (L)

[redacted]

12.6 Interim analyses

No formal interim analysis is planned for this study. The primary analysis will be performed after all patients have been treated for 6 months or have discontinued study treatment and afinal analysis will be performed after efficacy follow up is complete. Refer to Section 9.2.

12.7 Sample size calculation

12.7.1 Primary endpoint(s)

A total sample size of approximately 350 patients is planned for this study, randomly allocated in a 1:1 ratio between Arm 1 (175 patients) and Arm 2 (175 patients). Assuming an enrollment rate of 20 patients per month, the primary analysis cut-off would be expected to be approximately 24 months from the randomization of first patient. The sample size calculations are proposed such as to meet the non-inferiority margin of 0.814 with 80% power and one-sided 5% level of significance under the assumptions of an ORR of 48.3% in Arm 1 (experimental arm) and 43.9% in Arm 2 (control arm) and that 10% patients will not be evaluable for ORR. The details of operating characteristics are described below (EAST 6.3).

Table 12-2 Primary endpoint: Overall Response rate (ORR)

Ratio of ORR from Arm 1/Arm 2*	The ORR in Arm 1 based on the ORR ratio	Probability of lower 90% CI limit of the ratio of ORR Arm 1/ Arm 2> 0.814 *
1.1	48.3%	80.0%
1.05	46.1%	66.5%
1	43.9%	50.1%
0.95	41.7%	32.5%
0.9	39.5%	18.5%
0.814	35.7%	5.1%

* ORR in the control arm (Arm 2) is set to be 43.9% based on the pooled historical data from CLEE011A2301 and CLEE011E2301 (NSAI only).

For the calculation of non-inferiority margin, the ORRs of ribociclib in combination with NSAI vs NSAI alone were estimated by combining the historical 6-month overall response rate observed in patients with the measurable disease from the following two studies:

- Study CLEE011A2301, where ribociclib was investigated at a starting dose of 600 mg QD 3 week-on/1 week-off in combination with letrozole in postmenopausal women; and
- Study CLEE011E2301 (NSAI only) where ribociclib was investigated at a starting dose of 600 mg QD 3 week-on/1 week-off in combination with NSAI and goserelin in premenopausal women.

In both studies, the patient population is similar to the one proposed for this study, as all patients have HR-positive, HER2-negative advanced breast cancer with no prior treatment for advanced disease; and the ORRs are also very similar in CLEE011A2301 and CLEE011E2301 despite the difference in the menopausal status of study populations. The ORR up to 6-months was estimated to be 43.9% in ribociclib in combination with NSAI and 29.1% in NSAI alone by pooling patients with measurable disease from studies CLEE011A2301 and CLEE011E2301.

[redacted]

As such, the NI margin is calculated based on 50% retention on the log-scale of the ratio of 43.9% to 29.1%, which leads to the NI margin of 0.814 (FDA 2016).

12.7.2 Secondary endpoint(s)

The key secondary endpoint of the study is to evaluate if the upper 90% Confidence interval for the QTcF change from baseline at Cycle 1 Day 15 (2h post-dose) is less than 20 ms for the experimental dosing arm (Arm 1). Assuming that the ΔQTcF standard deviation is 20 ms, the probability of meeting this threshold under different scenarios of ΔQTcF at the Cmax is presented in Table 12-3.

Table 12-3 Operating characteristics for the key secondary endpoint: ΔQTcF at Cycle 1 Day 15 (2 h post-dose). Probability of the upper 90% CI < 20 ms under different value to True QTcF with a sample size of 175 patients in Arm 1

True mean (QTcF, ms)	Probability of upper 90% CI limit < 20 ms
15.5	90.6%
16	84.1%
17.5	50.0%
18	37.2%
18.8	19.9%
19.9	5.6%

12.7.3 Sample size considerations for PK analysis

Blood samples will be collected from all study patients for the analysis of plasma concentrations of ribociclib and assessment of ribociclib pharmacokinetics. In a subset of patients (~20 patients per arm), extensive PK blood sampling will be performed to provide approximate 12 evaluable patients to characterize PK per arm, and the PK collection schedule is specified in protocol Section 8.5.1.1.1. No hypothesis will be tested and therefore no specific sample size calculation has been performed. The choice of sample size and sampling time points were selected based on historical data and PK profile of ribociclib and is expected to represent the PK in the targeted treatment group.

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 International Conference on Harmonisation (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 study, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the study

[redacted]

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.

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 (*defined as last patient last visit*) and finalization of the study report the results of this study 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 study 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 (SOP) 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 study. 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.

[redacted]

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 informed 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.

[redacted]

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16 Appendices

16.1 Appendix 1 – Concomitant Medications

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 (DDI) 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//wwwfda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http//wwwdruginteractioninfo.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.

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, troleandomycinvoriconazole
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

[redacted]

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 or dietary supplements 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 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.

[redacted]

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, nortriptyline, nusinersen, ofloxacin, olanzapineosimertinib, 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

Category	Drug Name
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, zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, 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 16-1).
[6] Based on data 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.

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16.2 Appendix 2 - Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

Novartis Oncology

Clinical Development, Biometrics and Data Management, Drug Regulatory Affairs & Oncology Clinical Imaging

Study no: CLEE011A2207

Harmonization of Efficacy Analysis of Solid Tumor Studies

Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

Document type:	TA Specific Guideline
Document status:	Version 3.2: February 11, 2016 Version 3.1: November 29, 2011 Version 3: October 19, 2009 Version 2: January 18, 2007 Version 1: December 13, 2002
Release date:	11-Feb-2016
Authors (Version 3.2):	[redacted]
Authors (Version 3.1):	
Authors (Version 3):	
Authors (Version 2):	
Authors (Version 1):	

[redacted]

Table 16-3 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

[redacted]

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 16.2.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.2.3.2 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 16.2.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.2.2 Efficacy assessments

Tumor evaluations are made based on RECIST 1.1 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).

16.2.2.1 Definitions

16.2.2.1.1 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 16.2.3.2.9.

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 < 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions:

[redacted]

  - 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.

16.2.2.1.2 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 Overall Response Rate (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 16.2.3.2.9.

16.2.2.2 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,

[redacted]

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, LDH and Beta-hCG for testicular cancer) can be integrated

[redacted]

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 /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 stable disease (an effusion may be a side effect of the treatment) or progressive disease (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.

16.2.2.3 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 eCRF (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 16.2.2.1.1.
- **Nodal target**: See Section 16.2.2.1.1.

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 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.

[redacted]

16.2.2.4 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 16-4) and non-target lesions (Table 16-5) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-6) as well as the presence or absence of new lesions.

16.2.2.4.1 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.

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 subject 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.

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

[redacted]

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.

16.2.2.4.2 Determination of target lesion response

Table 16-4 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 16.2.2.2).

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 progressive disease
- 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 eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-4 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

[redacted]

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

[redacted]

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 SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.2.2.4.3 Determination of non-target lesion response

Table 16-5 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

[redacted]

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 16.2.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.2.2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion eCRF 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 16.2.2.5).

A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease 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 16.2.2.2.

16.2.2.5 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 16-6.

Table 16-6 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overalllesion 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.			

[redacted]

Target lesions	Non-target lesions	New Lesions	Overalllesion response
[3]As defined in Section 16.2.2.4 .			

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.

16.2.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.2.3.2.9 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.2.3.1 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:

[redacted]

- 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.

[redacted]

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 progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The time point 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).

[redacted]

16.2.3.2 Time to event variables

16.2.3.2.1 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, progression-free survival 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.

16.2.3.2.2 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.

16.2.3.2.3 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.

16.2.3.2.4 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 resensitizing 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

[redacted]

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.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues with respect to foreseeable censoring.

16.2.3.2.5 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.

16.2.3.2.6 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 duration of response 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 duration of response 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).

[redacted]

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.

16.2.3.2.7 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 overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 16.2.3.2.6. 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.

16.2.3.2.8 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

[redacted]

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 duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response 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 16.2.3.2.8).

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

[redacted]

16.2.3.2.9 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 non-measurable disease is derived slightly differently according to Table 16-7.

Table 16-7 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 16.2.2.4.

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.

16.2.3.2.10 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

[redacted]

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 SAP 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 16.2.3.2.7, 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 16-8 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

[redacted]

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
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 16.2.3.2.8.			
[2]After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.2.3.2.8.			
[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

[redacted]

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 16-8 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 SAP documentation.

16.2.4 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).

[redacted]

16.2.4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or SAP documentation. Any deviations from protocol must be discussed and defined at the latest in the SAP 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 SAP documentation before database lock).

16.2.4.2 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
- Subject/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment

Death is a reason which "*must*" lead to discontinuation of patient from trial.

16.2.4.3 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

[redacted]

- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.2.4.4 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 SAP 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.

16.2.4.5 Programming rules

The following should be used for programming of efficacy results:

16.2.4.5.1 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.

16.2.4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

[redacted]

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 16.2.3.2.7). 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.

16.2.4.5.3 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.

16.2.4.5.4 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)'.

16.2.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

16.2.4.5.6 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 16-8)
- 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 16.2.3.2.7. 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

[redacted]

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.

16.2.5 References (available upon request)

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