NOVARTIS

Clinical Development

Ribociclib (LEE011)

Oncology Clinical Protocol CLEE011A2404 / NCT02941926

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

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List of abbreviations

aBC	Advanced Breast Cancer
AE	Adverse Event
AI	Aromatase Inhibitors
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
ALP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
aBC	Advanced Breast Cancer
BC	Breast Cancer
BCRP	Breast Cancer resistance protein
BSEP	Bile export salt pump
CBD	Cannabidiol
CBR	Clinical Benefit Rate
CCND1	Cyclin D1
CDK4/6	Cyclin-Dependent Kinases 4 and 6
CMO&PS	Chief Medical Officer and Patient Safety
CL	Clearance
CNS	Central Nervous System
Cmax	Maximum Plasma Concentration
COA	Clinical Outcome Assessment
eCOA	Electronic Clinical Outcome Assessment
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DFS	Disease Free Survival
DHEA	Dehydroepiandrosterone
DI	Dose Intensity
DILI	Drug-Induced Liver Injury
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
ER	Estrogen Receptor
ET	Endocrine Therapy
FACT-B	Functional Assessment of Cancer Therapy - Breast
FAS	Full Analysis Set

[redacted]

FDA	Food and Drug Administration
FMO3	Flavin-containing Monooxygenase 3
FPFV	First Patient First Visit
FSH	Follicle Stimulating Hormone
G3/4	Grade 3/4
GCP	Good Clinical Practice
GI	Gastrointestinal
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HR+	Hormone Receptor Positive
IA	Interim Analysis
IB	Investigator's Brochure
IC50	Inhibitory Concentration, where 50% inhibition is observed
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IUD	Intrauterine Device
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LHRHa	Luteinizing Hormone-Releasing Hormone agonist
LLN	Lower Limit of Normal
LPFV	Last Patient First Visit
MATE1	Multidrug And Toxin Extrusion protein-1
NCCN	National Comprehensive Cancer Network
NSAI	Nonsteroidal Aromatase Inhibitors
NSCLC	Non-Small Cell Lung Cancer
OCT2	Organic Cation Transporter 2
OFS	Ovarian Function Suppression
ORR	Overall Response Rate
OS	Overall Survival
PAS	PRO Analysis Set
PD	Progression of Disease
P-gP	Permeability-glycoprotein
PFS	Progression Free Survival
PgR	Progesterone receptor
PHI	Protected Health Information
PK	Pharmacokinetics
pRb	Retinoblastoma Protein
PR	Partial Response
PRO	Patient-Reported Outcomes

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PS	Performance Status
PSDS	Post-Study Drug Supply
PT	Prothrombin Time
PTA	Post Trial Access
PVC	Premature Ventricular Contractions
QD	Quaque Die (every day)
QTcF	QT corrected interval using Fridericia
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
Rb	Retinoblastoma Protein
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RT	RadioTherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	Stable Disease
SERM	Selective ER Modulators
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	Half-life
TBIL	Total Bilirubin
TdP	Torsades de Pointes
TEN	Toxic Epidermal Necrolysis
THC	tetrahydrocannabinol
TTP	Time To Progression
ULN	Upper Limit of Normal
US	United States
VES	Visit Evaluation Schedule
WBC	White Blood Cell

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
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)
Investigational drug	The study treatment 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."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason.
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.

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Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent occurs only 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

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Protocol summary

Title	An open-label, multicenter, Phase IIIb study to assess the safety and efficacy of ribociclib (LEE011) in combination with letrozole for the treatment of men and pre/postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC) with no prior hormonal therapy for advanced disease
Brief title	Study to assess the safety and efficacy of ribociclib (LEE011) in combination with letrozole for the treatment of men and pre/postmenopausal women with HR+ HER2- aBC in a broader population
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this Phase IIIb study is to collect additional safety and efficacy data for the combination of ribociclib + letrozole in a broader population of patients with HR+HER2- aBC in comparison with other Phase III studies with ribociclib.
Primary Objective(s) and Key Secondary Objective	To evaluate the safety and tolerability of ribociclib with letrozole in men and pre/postmenopausal women with HR+, HER2- aBC who received no prior hormonal therapy for advanced disease Note: Throughout this document, perimenopausal and premenopausal status will be grouped together and referred as "Premenopausal"
Secondary Objectives	● To assess the clinical efficacy of ribociclib + letrozole measured by Time-to-Progression (TTP) and tumor response by overall response rate (ORR) and clinical benefit rate (CBR) ● To assess treatment impact on patient reported outcome (PRO) measured by variations of Functional Assessment of Cancer Therapy - Breast (FACT-B) questionnaire scores ● To evaluate long-term safety of ribociclib + letrozole during Extension Phase ● To evaluate clinical benefit of ribociclib + letrozole as assessed by investigator during Extension Phase
Study design	This open-label, single arm, multi-center Phase IIIb study will evaluate the overall safety and tolerability and clinical efficacy of ribociclib in combination with letrozole in men and pre/postmenopausal women with HR+, HER2- aBC and no prior hormonal treatment for advanced disease. A total of approximately 3,000 patients will be enrolled for treatment with Letrozole (2.5 mg once daily) + Ribociclib (LEE011) 600 mg (day 1 to 21 in a 28 day cycle); goserelin (3.6mg as injectable subcutaneous implant every 28 days) or leuprolide (7.5mg intramuscular injection every 28 days) will be used in men and premenopausal women patients. The study will be composed of 2 phases: Core Phase (from FPFV to 18 months after LPFV) and Extension Phase (18 months from LPLV of the Core Phase). During the Core Phase, safety and efficacy data (including ePRO in selected countries) will be collected. In the event that patients are still deriving benefit at the end of the Core phase and ribociclib is not approved or available and reimbursed, patients may be transitioned to the Extension Phase and continue to receive study treatment until progression, intolerance, death or physician/patient decision. Only safety and clinical benefit (as assessed by investigator) data will be collected in the Extension Phase During the Extension Phase, if ribociclib is approved and reimbursed, patients will be transitioned to prescription or drug access/support program(s) according to local laws and regulations. The study will end after completion of the Extension Phase and all remaining patients will discontinue from the study. Patients who complete this Extension Phase, and continue to derive clinical benefit from the treatment based on the investigator's evaluation will receive ribociclib from prescription (if approved and

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	reimbursed), another Post-Trial Access (PTA) program, or other drug access/support program(s).
Population	This study includes men and pre/postmenopausal women with HR+, HER2- aBC who had not received any prior hormonal agent for treatment of advanced disease

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Inclusion criteria	1. Patient is an adult, male or female ≥ 18 years old at the time of informed consent 2. Male or female with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy. 3. In the case of women, both pre/perimenopausal and postmenopausal patients are allowed to be included in this study; menopausal status is relevant for the requirement of goserelin or leuprolide to be used concomitantly with ribociclib and letrozole. a) Postmenopausal status is defined either by: i) Prior bilateral oophorectomy OR ii) Age ≥60 OR iii) Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range. If patient is taking tamoxifen or toremifene and age <60, then FSH and plasma estradiol levels should be in post-menopausal range per local normal range. Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure menopausal status. b) Premenopausal status is defined as either: i) Patient had last menstrual period within the last 12 months OR ii) If on tamoxifen or toremifene within the past 14 days, plasma estradiol and FSH must be in the premenopausal range per local normal range OR iii) In case of therapy induced amenorrhea, plasma estradiol and/or FSH must be in the premenopausal range per local normal range. c) Perimenopausal status is define as neither premenopausal nor postmenopausal Note: Throughout this document, perimenopausal and premenopausal status is grouped together and referred as “Premenopausal” 4. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory. A confirmatory biopsy is not required. 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. 6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 7. Patient has adequate bone marrow and organ function as defined by ALL of the following laboratory values (as assessed by local laboratory): ● Absolute neutrophil count ≥ 1.5 × 109/L ● Platelets ≥ 100 × 109/L ● Hemoglobin ≥ 9.0 g/dL ● Potassium, sodium, calcium corrected for serum albumin and magnesium within normal limits or corrected to within normal limits with supplements before first dose of the study medication ● INR ≤1.5 ● Serum creatinine <1.5 mg/dl or creatinine clearance ≥ 50 mL/min

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	● In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be < 2.5 × ULN. If the patient has liver metastases, ALT and AST should be < 5 × ULN. ● Total bilirubin < ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN. 8. Patient must have a 12-lead ECG with ALL of the following parameters at screening: ● QTcF interval at screening < 450 msec (using Fridericia's correction) ● Resting heart rate ≥ 50 bpm 9. Patient must be able to swallow ribociclib and letrozole tablets 10. Patient has signed informed consent obtained before any trial-related activities and according to local guidelines 11. Patients must be able to communicate with the investigator and comply with the requirements of the study procedures
Exclusion criteria	1. Patient has a known hypersensitivity to any of the excipients of ribociclib or letrozole, including peanut and soy 2. Patient who received any CDK4/6 inhibitor 3. Patient who received any prior systemic hormonal therapy for advanced breast cancer; no more than one prior regimen of chemotherapy for the treatment of metastatic disease is permitted Note: ● Patients who received (neo) adjuvant therapy for breast cancer are eligible. If the prior neo (adjuvant) therapy included letrozole or anastrozole the disease free interval must be greater than 12 months from the completion of treatment until study entry. ● Patients who received ≤ 28 days of letrozole or anastrozole for advanced disease prior to inclusion in this trial are eligible. 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 side effects 6. Patient who has not had resolution of all acute toxic effects of prior anti-cancer therapy to NCI CTCAE version 4.03 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion) 7. Patient who has received extended-field radiotherapy ≤ 4 weeks or limited field radiotherapy for palliation ≤ 2 weeks prior to start of treatment, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia) and/or from whom ≥ 25% (Ellis RE 1961) of the bone marrow has been previously irradiated are also excluded. (see Appendix 14.4) 8. Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer 9. Patient with central nervous system (CNS) metastases unless they meet ALL of the following criteria: ● At least 4 weeks from prior therapy for CNS disease completion (including radiation and/or surgery) to starting the study treatment. ● Clinically stable CNS lesions at the time of study treatment initiation and not receiving steroids and/or enzyme-inducing anti-epileptic medications for the management of brain metastases for at least 2 weeks. 10. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., uncontrolled

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	ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) 11. Patient has a known history of HIV infection (testing not mandatory) 12. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol: (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.) 13. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including but not limited to any of the following: ● History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening ● History of documented congestive heart failure (New York Heart Association functional classification III-IV) ● Documented cardiomyopathy ● 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) ● Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following: i. Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia. ii. Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication iii. Inability to determine the QTcF (Fridericia's correction) interval on screening ● Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening 14. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to starting Cycle 1 Day 1: ● Concomitant medications, herbal supplements, and/or fruits (e.g. grapefruit, pumeloes, star fruit, Seville oranges) and their juices that are known strong inducers or inhibitors of CYP3A4/5 (See Appendix 14.1) ● Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5 15. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular) 16. Participation in a prior investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longer 17. Pregnant or nursing (lactating) women Note: Women of child-bearing potential is defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 21 days after stopping your study medication. 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,

[redacted]

	symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception ● Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy (surgical removal of the uterus and cervix) or tubal ligation (getting the "tubes tied") at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment ● Male partner sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient ● Placement of an intrauterine device (IUD) or intrauterine system (IUS) Note: Use of oral (estrogen and progesterone), transdermal, injected, implantedhormone containing intrauterine (IUS) or any other hormonal methods of contraception is not allowed in this study
Investigational and reference therapy	Ribociclib 600mg oral daily (3 weeks on/ 1 week off) in combination with letrozole 2.5 mg oral once daily; goserelin 3.6mg (as injectable subcutaneous implant every 28 days) or leuprolide 7.5mg (as injectable intramuscular depot every 28 days) will be used in men and premenopausal women patients
Safety assessments	● Physical examinations ● ECOG performance status ● Weight and vital signs ● 12 lead ECGs (assessed locally) ● Laboratory assessments including hematology, chemistry and INR (assessed by local lab) ● Adverse Events (AEs) collection
Efficacy assessments	Clinical efficacy will be assessed by the investigator Tumor assessments will be performed according to the current standard of care (every 12 weeks until disease progression is recommended)
Other assessments	Patient Reported Outcomes FACT-B Questionnaire (See Appendix 14.2)
Data analysis	The data will be summarized with respect to demographic and baseline characteristics, and safety observations and efficacy measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Time to progression (TTP) is defined as time from date of start of treatment to the date of event defined as the first documented progression or death due to underlying cancer (Appendix 14.3: Novartis RECIST Guideline v 3.2). ORR and CBR will be calculated and summarized based on investigators' assessment (according to RECIST 1.1). For PROs, descriptive statistics will be used to summarize the subscale and overall scores at each scheduled assessment time point. Additionally, change from baseline at the time of each assessment will be summarized.
Key words	HR-positive, HER2-negative, advanced breast cancer, LEE011, ribociclib, letrozole, goserelin, leuprolide, CDK, CDK4, CDK6, CDK4/6, Phase IIIb, ER-positive, PR-positive, premenopausal, postmenopausal, male breast cancer

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Amendment 04 (23-Jan-2020)

Amendment Rationale

The study was initiated in November, 2016 and 3,246 subjects were treated. The Core Phase was completed (Last Patient Last Treatment occurred on 09-Oct-2019 and Last Patient Last Visit occurred on 08-Nov-2019). A total of 415 subjects have been transitioned to the Extension Phase of the study.

The current amendment is intended to incorporate the updated safety information on ribociclib in alignment with LEE011 (Ribociclib) Investigator's Brochure (IB), Edition 14 (release date: 28-Nov-2019) and to define the duration of the Extension Phase and transition plan for patients during and at the end of the study .

- Interstitial Lung Disease (ILD)/pneumonitis has been observed with CDK4/6 inhibitor treatment as a class effect and was requested by FDA to be added to US label (Please refer to IB Edition 14 for more information). A new 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 Edition 14 for more information). Protocol section 6.3.1.3.5, Guidance for all other adverse reactions was updated with clear guidance to discontinue ribociclib if TEN is diagnosed
- Updated recommended tables relating to Hepatic and Cardiac QTc Monitoring
- Clarified Contraceptive methods allowed during study
- Updated the list of prohibited medications during study treatment, and co-medication considerations
- Updated the list of medications to be used with caution during study drug treatment
- Updated the language regarding Extension Phase duration and transition plan
- Editorial and typographical 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 underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Protocol Summary Exclusion criterion 17 clarified the information provided on acceptable male and female contraception methods by:
  a. Removal of the needed combination of an IUD/IUS with an occlusive cap or condom with spermicidal foam/gel/film/vaginal suppository
  b. Additional methods of hormone contraceptives not allowed in the study
- Section 4.3 was updated to clarify the end of the Extension Phase and transition plan
- Table 6-3 was updated by removal of Grade 3 ANC without fever or signs of infection on Day 14 of the first 2 cycles

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- Table 6-3 Title was updated with CTCAE v4.03 grading
- Table 6-4 Title was updated with CTCAE v4.03 grading and clarification of bi-weekly to every two weeks
- Table 6-5 was updated with instructions on how to manage Grade 2 QTc prolongation with instructions to repeat ECG within one hour of first QTcF ≥ 481 ms
- Section 6.3.1.3.4 and Table 6-6 Ribociclib dose adjustment and management recommendation for ILD/pneumonitis was added in.
- Former section 6.3.1.3.4 Guidance for all other adverse reactions was renumbered to 6.3.1.3.5
- Former Table 6-6 was renumbered to Table 6-7 Ribociclib dose reduction/interruption and management recommendation for all other adverse reactions
- Table 6-7 Ribociclib dose reduction/interruption and management recommendation for all other adverse reactions include language referring to Toxic Epidermal Necrosis (TEN) was modified
- Section 6.4.1 updated the text with with prohibited medications and the list of use with cautions with citations for Appendices
- Section 6.4.1.3 Palliative Radiotherapy wording clarified that RT should not be used on target lesions and the total cumulative doses should not encompass > 25% of irradiated bone marrow
- Section 6.4.1.3 text moved to the Section 6.4.4 ie, 'Refer to the ribociclib [Investigator's Brochure] and letrozole, goserelin, and leuprolide drug package insert and Appendix 14.1 for information on possible interactions with other drugs'
- Former Table 6-7 was renumbered to Table 6-8 Package and labeling
- Former Table 6-8 was renumbered to Table 6-9 Supply and Storage of Study Treatment
- Table 7-2 Extension Phase Visit Evaluation Schedule was revised to label visits E-C1D1, E-C4D1, E-C7D1, and E-C1D1 and subsequent cycles and goserelin/leuprolide dose administration updated to monthly
- Section 7.1.5 was updated to describe discontinuation of study treatment from the Extension Phase
- Section 8.4 Pregnancies was updated to remove the timeframe for outcome collection for pregnant partners of male patients
- Section 14.1 - Appendix 1 cited source changed from 'Oncology Clinical Pharmacology guidance' to 'Novartis PK Science Memorandum' and the release updated to Jan 2018
- Table 14-1 was updated with the most current prohibited medications
- Table 14-2 was updated with the most current medications to be used with caution

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.

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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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Amendment 03 (24-Sep-2018)

Amendment Rationale

The study was initiated in November, 2016 and enrollment has been completed (last Patient First Visit occurred on March 22, 2018). 3255 patients have been enrolled in the study.

The current amendment is intended to incorporate updated ribociclib program information.

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

- Updated the language regarding early study termination by the sponsor
- Updated withdrawal of consent language with the new Global Data Protection Requirements
- Updated the dose adjustment and management recommendations for QTcF prolongation. Analyses of preclinical and clinical data with ribociclib have demonstrated that ribociclib prolongs the QT interval in a concentration-dependent manner. Moreover, based on the ribociclib exposure-ΔQTcF relationship and the clinical experience in studies CLEE011A2301 (MONALEESA-2), CLEE011F2301 (MONALEESA-3) and CLEE011E2301 (MONALEESA-7), ribociclib dose reduction is an effective strategy for managing ribociclib therapy in patients experiencing QTcF prolongation. Therefore, in order to reduce the risk of subsequent QTcF prolongation in patients experiencing a QTcF between 481-500 msec, ribociclib dosing should be reduced by 1 dose level with the first occurrence of QTcF $\geq$ 481 msec. As a result, this amendment includes an update to the dosage management guidance for patients who experience QTc prolongation.
- Updated the list of prohibited medications during study treatment, and co-medication considerations
- Updated the list of medications to be used with caution during study drug treatment
- Clarified that paper PROs may be used if ePRO is unavailable
- Editorial and typographical 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 underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Protocol Summary inclusion criterion 1 removed the need for men to use a condom while taking drug and for 21 days after stopping medication, whether they are vasectomized or not.
- Protocol Summary exclusion criterion 17 expanded the information provided on acceptable female contraception methods
- Section 4.4 updated the language regarding the reasons why the study may be terminated early by the sponsor and what actions are needed in that case
- Section 5.2 inclusion criterion 1 removed the need for men to use a condom while taking drug and for 21 days after stopping medication, whether they are vasectomized or not.

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- Section 5.3 exclusion criterion 17 expanded the information provided on acceptable female contraception methods
- Sections 6.1.1.1 and 6.4.3 updated to clarify that herbal or dietary supplements with a known risk of QT prolongation are not permitted
- Section 6.4.1.4 updated to indicate that potential drug interactions are possible between ribociclib and antiemetics.
- Section 6.4.2 clarified the information provided regarding renal transporters MATE1, OCT2 and BCRP.
- Section 6.4.3 was updated to clarify that both herbal medications and dietary supplements that are strong inhibitors of CYP3A4/5 or those known to cause QT prolongation are prohibited.
- Section 7.1 and table 7.5 were updated to clarify that absolute lymphocyte count is required when reporting hematology-related lab results
- Section 7.1.6 was updated with updated language regarding actions needed when a patient withdraws their consent to participate in the trial
- Section 7.2.3 was updated to clarify the timing of the PRO administration
- Section 8.1.3 was removed due to redundancy as AESI review information is also included in section 10.4.1
- Section 9.3.2 was updated to allow for use of paper PROs when the ePRO is unavailable, and to clarify that questionnaires should be administered in the patient's local language
- Table 6-5 was updated with instructions on how to manage QTcF prolongation
- Table 14-1 was updated with the most current prohibited medications
- Table 14-2 was updated with the most current medications to be used with caution

IRBs/IECs

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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.

[redacted]

Amendment 02 (16-Aug-2017)

Amendment rationale

The study was initiated in November, 2016 and enrollment is currently ongoing. As of Aug 8, 2017, 1008 patients have been enrolled in the study.

The current amendment is intended to update the existing information on ribociclib and clarify specific aspects of amendment 01, based on feedback and communications received from investigators and the Study Steering Committee. This will result in enhanced clarity for patient eligibility and quality of data collection.

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

- Information from the pivotal study CLEE011A2301 (MONALEESA-2) supporting the use of ribociclib + letrozole in aBC has been updated to strengthen the study rationale
- Standard language around contraception was updated in the inclusion/exclusion criteria
- Recruitment duration was adjusted according to the expected recruitment figures and required follow-up to adequately address the primary and secondary objectives of the study
- Clarifications on assessments performed during the Core Phase and the Extension Phase
- Expansion of another monthly-based dosing LHRH agonist (leuprolide) in addition to goserelin, based on NCCN Breast Cancer Guidelines 2017
- Removal of requirement for prior anti-cancer therapy 5 half-lives washout period, given the low probability of drug-drug interactions and the urgency to treat patients with advanced breast cancer who are progressing
- Clarified radiotherapy windows and rationale
- Additional clarification and updated wording on prohibition of herbal products
- Updated wording on allowance of local/regional sub-studies/analysis studies
- Clarification about ribociclib administration and assessments schedule due to drug interruptions from adverse events
- Clarification of the sample size calculation. Three thousand (3,000) patients are planned to be enrolled in this study to detect rare AEs (frequency ~0.1%) with high probability. This will allow for a greater precision when reporting rare, but clinically meaningful AEs (e.g. febrile neutropenia, QT prolongation, renal insufficiency, thromboembolic events, etc.) and will allow for a meaningful safety analysis of specific patient subgroups of particular interest

Amendment 02 also includes minor editorial changes and additional clarifications to address investigators' questions as described in the list of changes below.

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 underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

[redacted]

- Cover page authorship was removed according to Novartis Oncology Protocol template, version 06-Apr-2017
- Summary section of the protocol has been updated to maintain consistency with the main body of the protocol
- Section 1.1.1 updated current preclinical and clinical data supporting CDK4/6 pathway in breast cancer
- Section 1.1.3 role of Cyclin D kinases inhibitor in breast cancer was deleted as updated information was provided in Section 1.1.1
- Section 1.2.1 overview of ribociclib was updated with newly reported results on non-clinical data, clinical safety, clinical efficacy, clinical pharmacokinetics, and clinical experience
- Section 1.2.4 summary of results from study CLEE011X2107 and Section 1.2.5 summary of results from study CLEE011A2301 was removed as the updated information has been provided in the updated Section 1.2
- Section 1.2.6 was updated with LHRH agonists information and was renumbered as Section 1.2.4
- Section 1.2.7 was removed
- Section 2.4 (previous) was deleted and merged with Section 2.3: rationale for dose and regimen selection updated; added leuprolide to the combination of ribociclib+letrozole to achieve adequate hormonal suppression in men/premenopausal women
- Section 2.6 renumbered as Section 2.5: added ribociclib approval by US FDA on Mar 13, 2017
- Section 4.1 updated to allow the use of leuprolide; removed expected Core Phase duration of 36 months; allowed local/regional sub-studies/analysis to be conducted in patient population enrolled in LEE011A2404 study; Figure 4-1 study design was updated to allow the use of leuprolide for ovarian suppression
- Section 4.3 revised definition of end of study
- Section 5.2 inclusion criterion 4 clarified that a confirmatory biopsy is not required
- Section 5.2 inclusion criterion 7 clarified the laboratory values required for total bilirubin and direct bilirubin
- Section 5.3 exclusion criterion 3 removed requirement of stopping any prior (neo)adjuvant anti-cancer therapy or prior chemotherapy for metastatic disease at least 5 half-lives or 7 days before study entry
- Section 5.3 exclusion criterion 7 clarified the criterion on prior radiotherapy
- Section 5.3 exclusion criterion 14 clarified prohibition of herbal products
- Section 5.3 exclusion criterion 17 updated highly effective contraception methods
- Section 6.1, Section 6.1.1, Table 6-1, Figure 6-1, and Section 6.1.1.1 updated with leuprolide dose and treatment information
- Section 6.1.5 Treatment Duration was revised to remove the 18 months of recruitment period after FPFV
- Section 6.3.1 clarified dose modifications and discontinuations guides for ribociclib, letrozole, and goserelin/leuprolide

[redacted]

- Section 6.3.1.2 updated dose information and monitoring of post-menopausal status of patient given LHRH agonists
- Section 6.3.1.3 Table 6-2 Dose Modification Guideline: Letrozole and Goserelin columns were removed from table; clarified seven consecutive rest days needed prior to reinitiating ribociclib
- Section 6.3.1.3.1 Added Recommendations on Adjustment of Ribociclib Treatment Cycles in the Case of Dose Interruptions/ Reinitiation
- Section 6.3.1.3.2 Follow up on potential drug-induced liver injury (DILI) cases was renumbered from former Section 6.3.1.3.1
- Section 6.3.1.3.3 Additional follow-up for QTc prolongation was renumbered from former Section 6.3.1.3.2
- Table 6-3 clarified dose adjustment and management recommendation on Absolute Neutrophil Count (ANC) Grade 4 toxicity
- Table 6-4 modified dose reduction/interruption and management recommendation for Grade 2 and 3 hepatotoxicity and note section
- Section 6.1.3.4 adjustment of starting dose in special populations was removed as this protocol is not intended to investigate the combination of ribociclib + letrozole in the special populations
- Section 6.4.1 clarified requirement of documenting dose schedule change of concomitant medications
- Section 6.4.1.2 clarified that the prophylactic use of WBC growth factors with ribociclib is not recommended as ASCO guidelines recommendations regarding the use of WBC growth factors is for chemotherapy induced neutropenia
- Section 6.4.1.4 added the use of antiemetic medications
- Section 6.4.2 updated the use of permitted concomitant therapy requiring caution
- Section 6.4.3 clarified the use of prohibited concomitant therapy
- Section 6.4.4 updated the use of drugs with QT prolongation as concomitant medications
- Section 6.6 added leuprolide information on drug dispensing, packaging and labeling, and drug supply and storage
- Section 7.1 clarified direct bilirubin required to be assessed at screening and during treatment only if clinically indicated; clarified that study visits should be adjusted according to treatment cycle in the case of ribociclib being withheld
- Section 7.1.2 updated to allow bloodwork completed during regular work-up as standard practice within 5 calendar days prior to signing ICF to be considered as screening assessments
- Section 7.1.4 updated with leuprolide information
- Section 7.1.5 clarified patients' withdrawal/discontinuation criteria and EOT visit schedule
- Section 7.2.2.5.4 renamed section Pregnancy and Hormonal Levels and clarified FSH and Estradiol local collection (not collected on eCRFs) at screening for confirmation on menopausal status

[redacted]

- Table 7-1 Visit Evaluation Schedule updated Chemistry and Coagulation reference link to Table 7-5; added leuprolide to table; for hematology and chemistry assessments during screening, added text "-14 days to Day 1". This 14 day period was already part of the protocol in Section 7.2.2.5
- Table 7-5 clarified direct bilirubin required only if clinically indicated, added note to clarify that electrolytes are required to be monitored but not entered on the eCRF
- Table 7-6 clarified FACT-B questionnaires collection plan to include End of Treatment visit
- Sections 8.2.2 and 8.4 replaced "Novartis Drug Safety and Epidemiology (DS&E)" with "Novartis Chief Medical Office and Patient Safety (CMO&PS)"
- Section 8.4 replaced "must" with "should" for collection of pregnancy outcomes of female partners' of male participants
- Section 10.1.3 added to clarify safety set in Extension Phase
- Section 10.3 clarified safety set analysis in Core Phase and Extension Phase respectively
- Section 10.5.3.1 clarified safety set used for safety analysis in Core Phase and Extension Phase respectively during pre-treatment, on-treatment, and post-treatment period
- Section 10.7 clarified interim analysis plan
- Section 10.8 clarified sample size calculation
- Table 10-1 added to show confidence intervals associated with AEs of interest for subgroups
- Section 14.1 Prohibited Concomitant Medications and Concomitant Medication use with Caution medications were updated; Website www.qtdrugs.org was updated to www.crediblemeds.org
- References section updated

IRBs/IECs

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Amendment 01 (19-Dec-2016)

Amendment rationale

The study was initiated in Nov, 2016 and enrollment is currently ongoing with First Patient First Visit (FPFV) on 30-Nov-2016.

The current amendment is intended to update the existing information about ribociclib, clarify specific aspects of the original protocol and expand the patient population to also include premenopausal women in use of ovarian suppression with goserelin. A summary of the key changes proposed in this amendment is listed below:

- Ribociclib information was updated based on the data available on the current IB version (v10, release date: Oct-10-2016; safety cut-off date: Jul-5-2016)
- Detailed information from the pivotal study CLEE011A2301 (MONALEESA-2) supporting the use of ribociclib + letrozole in aBC has been included to strengthen the study rationale
- Premenopausal patients (receiving concomitant ovarian suppression with goserelin) are allowed to be included in the study, based on current treatment guidelines suggesting similar treatment strategies in premenopausal patients with ovarian suppression as post-menopausal patients and data from another CDKi (palbociclib) demonstrating similar efficacy of CDKi + ET in prepost-menopausal patients (PALOMA-3 Study). Standard language around contraception was added to the inclusion/exclusion criteria as of result of this change
- Male patients entering the study will also be required to use goserelin concurrently with ribociclib + letrozole based on the current standard of care in this patient population and to avoid potential increase of FSH and testosterone (increasing potential substrates for aromatization) which could be associated with prolonged administration of AIs
- Recruitment duration and follow-up duration were adjusted according to the expected recruitment period and required follow-up to adequately address the primary and secondary objectives of the study
    - Recruitment will be completed 18 months after FPFV or when 3,000 patients are enrolled, whichever occurs first
    - Core Phase of the study will be completed 18 months after LPFV
- Core Phase (from FPFV to 18 months after Last Patient First Visit (LPFV)) and Extension Phase (18 months after LPFV to Last Patient Last Visit (LPLV)) of the study is defined
- Clarifications on assessments performed during the Core Phase and the Extension Phase
- Clarifications around the use of denosumab and bisphosphonates, which are now allowed together with ribociclib + letrozole according to investigator's judgment
- Adjustments of VES requiring study visits every 2 months after 6 months of treatment (starting on C6), and every 3 months after 12 months of treatment (starting on C12).

Amendment 01 also includes minor editorial changes and additional clarifications to address investigators' questions as described in the list of changes below.

[redacted]

Changes to the protocol

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The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Throughout the document: Addition of language to refer to most recent version of the LEE011 Investigator's Brochure and minor text editorial changes
- Throughout the document: Premenopausal and perimenopausal status is grouped together and referred as "Premenopausal"
- Throughout the document: Typographical and grammatical corrections
- Section 1: Updated based on new data from ongoing and completed trials with LEE011.
- Section 1.1.2: Updated to include data on clinical benefit of AIs in combination with ovarian function suppression (OFS) in premenopausal patients with breast cancer in neoadjuvant, adjuvant and advanced settings; Rationale for inclusion of male patients is further clarified.
- Section 1.2.5: Added to provide CLEE011A2301 (MONALEESA-2) trial key efficacy and safety results of pre-planned interim analysis.
- Section 1.2.6 and Section 1.2.7: Added to provide information on Goserelin (Zoladex®) overview and drug-drug-interactions.
- Section 2: Added rationale on inclusion of premenopausal patients with appropriate ovarian suppression (with the use of goserelin) in this trial. Study rationale was updated with CLEE011A2301 (MONALEESA-2) positive interim result to reinforce the activity of the combination of ribociclib and letrozole.
- Section 2.4: Addition of rationale for the standard dose of goserelin.
- Section 2.5: Addition of rationale for non-comparative design.
- Section 2.6: Risks and benefits section was updated in relation to CLEE011A2301 (MONALEESA-2) positive interim result and addition of goserelin to premenopausal/ male patients.
- Section 3 Table 3-1: updated to add secondary objective for Extension Phase and the associated end points.
- Section 4.1: Updated to define Core and Extension Phase of the study; added Extension Phase to allow patients who still derive benefit of ribociclib-based treatment however without access to ribociclib to continue to receive treatment until EOT; updated to clarify that goserelin is added to the treatment regimen in men/premenopausal women patients. Clarification was provided to allow country to stop recruitment after the planned number of patients is reached in respective country during the study.
- Figure 4-1: Updated to add Extension Phase of the study; updated to add goserelin to the study treatment (ribociclib+letrozole+goserelin) for male and premenopausal patients. "Study treatment" was updated as appropriate throughout the document.
- Section 4.3: Definition of end of study was revised to clarify on recruitment period (18 months) and end of Core Phase (18 months after LPFV).

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- Section 5.2: Inclusion criterion #3 was updated to include pre/perimenopausal women with premenopausal status defined; additionally, postmenopausal status is further clarified in the case of age < 60 if patient is taking tamoxifen or toremifene.
- Section 5.3: Exclusion criterion #17 was added to require premenopausal women to use highly effective contraception method during the study.
- Section 6.1 and Section 6.1.1: Updated to add goserelin to study treatment for men and premenopausal women. Figure 6-1 dosing regimen was updated to include goserelin.
- Section 6.1.5: Treatment duration was updated and further clarified in relation to Core Phase and Extension Phase of the study.
- Section 6.3.1: Clarified that dose reduction is not permitted for letrozole and goserelin. Robociclib dose modification guidelines were clarified to ensure seven (7) consecutive rest days and avoid overdose.
- Section 6.3.1.3.4: Updated dose modification guidelines on adjustment of starting dose in renal impairment and hepatic impairment populations.
- Table 6-2: Goserelin was added to Table 6-2 Dose Modification Guidelines
- Table 6-3: Ribociclib dose reduction/interruption guidelines updated for G3 neutropenia on Day 14 of the first 2 cycles.
- Section 6.4.1.1: Clarified that the use of denosumab and bisphosphonates together with ribociclib+ letrozole is allowed according to investigator's judgement.
- Section 6.6: Updated to include goserelin information on study drug preparation and dispensation, study treatment packaging and labeling, and drug supply and storage.
- Table 7-1 Visit Evaluation Schedule (VES) was updated as Core Phase VES. Other clarifications and updates include: clarifications of pregnancy test requirement, adjustments on the schedule of ribociclib IRT dispensing, ePRO, vital sign and weight, ECOG, and physical exam assessment schedules were adjusted to monthly for C1-C5, every 2 months for C6-C11, and every 3 months from C12 onwards; updates on the requirement of EOT visit completion within 7 days from the last ribociclib based treatment.
- Section 7.1.4: Added Extension Phase.
- Section 7.1.5: Added discontinuation information on Core Phase. Table 7-2: Added Extension Phase VES.
- Section 7.1.7: Follow-up for safety evaluation was updated to clarify the requirement after EOT of Core and Extension Phase.
- Section 7.2.1: Clarification on no central review of imaging assessments; Confirmation of Clinical Benefit is required during the Extension Phase.
- Section 7.2.2: Addition of safety assessments required during Extension Phase.
- Section 7.2.3: Clarified that FACT-B is collected electronically in selected countries and it is not collected on male patients.
- Section 7.2.2.5.4: Pregnancy section is added.
- Table 7-5: Pregnancy test is added.
- Section 10: Updated to add data summary at Extension Phase and details in subgroup analysis.

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- Section 10.4.1: Updated to clarify the variables to evaluate the primary objective.
- Section 10.5.1: updated to add secondary objective for Extension Phase.

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1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Role of the CDK4/6 pathway in breast cancer

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

Cell cycle progression is regulated by cyclin-dependent serine-threonine protein kinases (CDKs). Extracellular growth and adhesion signals increase the level and function of cyclin D proteins within the cell. In turn, the cyclin D proteins associate with and activate CDK4 and CDK6 (Musgrove et al 2011). CDK4 and CDK6 phosphorylation leads to inactivation of the retinoblastoma protein (Rb) and thus releases E2F, which in turn leads to the transcription initiation of proteins involved in cell cycle propagation and proliferation (Figure 1-1). 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; The Cancer Genome Atlas Network 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 is common in BC, and in all cancers in general, and 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 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 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 and ribociclib, inhibit proliferation and induce apoptosis in preclinical models of endocrine-resistant breast cancer (Miller et al 2011; Thangavel et al 2011; ribociclib [Investigator's Brochure]. Both palbociclib and ribociclib demonstrated synergy with endocrine treatments in preclinical studies and efficacy in clinical studies in patients with HR-positive, HER2-negative advanced BC (Finn et al 2009; ribociclib [Investigator's Brochure]). Addition of palbociclib to letrozole improved median progression-free survival (PFS) from 10.2 months to 20.2 months (hazard ratio 0.49, 95% CI: 0.32-0.75, p=0.0004) in a randomized, open-label, multicenter phase II study (Finn et al 2015) and from

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14.5 to 24.8 months (hazard ratio 0.58, 95% CI: 0.46-0.72, p=0.0001) in a phase III study in systemic non-adjuvant treatment-naïve postmenopausal women with ER-positive, HER2-negative advanced BC (Finn et al 2016). In addition, in a phase III study in 521 pre- and postmenopausal patients with advanced HR-positive, HER2-negative BC that had relapsed or progressed during prior ET, addition of palbociclib to fulvestrant (with ovarian suppression in premenopausal women in both arms) improved median PFS from 3.8 months to 9.2 months (hazard ratio 0.42; 95% CI: 0.32-0.56; p<0.001) (Turner et al 2015).

In the subgroup analysis of this study, the palbociclib-containing regimen has similar efficacy in pre-/perimenopausal vs post-menopausal women and PFS results were not significantly associated with plasma estrogen (E2) levels (Loibl et al 2016), supporting use of palbociclib in pre-/perimenopausal women.

Efficacy and safety of the combination of ribociclib and letrozole as first line treatment was evaluated in 668 postmenopausal women with HR-positive, HER2-negative advanced BC in a phase III study (CLEE011A2301). Ribociclib significantly improved PFS (hazard ratio 0.56, 95% CI: 0.43-0.72, p = 0.00000329) (Hortobagyi et al 2016).

Refer to the most recent ribociclib [Investigator's Brochure] for more details.

An update to this study with an additional 11 months of follow-up reported a consistent improvement in PFS in comparison with the interim analysis. Median PFS was prolonged by 9.3 mo, from 16.0 mo (95% CI: 13.4–18.2) in the placebo + letrozole arm to 25.3 mo (95% CI: 23.0–30.3) in the ribociclib + letrozole arm (hazard ratio 0.568, 95% CI: 0.457-0.704, p=0.0000000963). 24-mo PFS rates were 54.7% vs 35.9%. The investigator-reported overall response rate was 42.5% (95% CI: 37.2%-47.8%) in the ribociclib arm and 28.7% (95% CI: 23.9%-33.6%) in the placebo arm (in the full analysis set); and 54.5% (95% CI: 48.4%, 60.6.%) and 38.8% (95% CI: 32.7%, 44.9%) in patients with measurable disease at baseline (Hotobagyi et al, ASCO 2017).

Considering demonstrated efficacy of CDK4/6 inhibitors in the HR-positive, HER2-negative advanced BC, 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.

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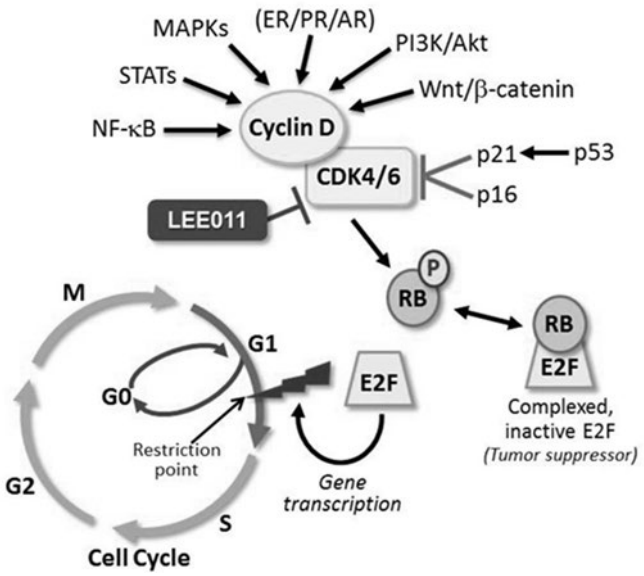
Figure 1-1 Regulation of cell cycle checkpoint control



Adapted from Lange and Yee 2011.

Refer to ribociclib [Investigator's Brochure] for more details.

1.1.2 Role of estrogen pathway in breast cancer

Expression of the estrogen receptor (ER) and/or progesterone receptor (PgR) is one of the most important prognostic factors in invasive breast cancer and is detected in approximately 70% of cases. Estrogen deprivation therapy is the core treatment modality in patients with hormone receptor positive (HR+) advanced breast cancer.

Endocrine therapy options for postmenopausal women with ER+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer) include selective ER modulators or SERM (tamoxifen), ER antagonists (fulvestrant), nonsteroidal aromatase inhibitors (NSAI; anastrozole and letrozole) and steroidal aromatase inhibitors (exemestane). Blocking estrogen signaling with tamoxifen has been the main approach in treatment for ER^+ breast cancer for over 35 years. In postmenopausal women, aromatase inhibitors (AI) reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens in non-ovarian tissues; synthesis in these tissues is the primary source of estrogens in postmenopausal women. AIs are generally used as the first line of therapy for women with HR+ breast cancer (Beslija 2009; NCCN 2.2017).

In premenopausal patients without previous exposure to an antiestrogen, initial treatment of advanced/metastatic disease involves the use of a selective ER modulator alone or ovarian suppression/ablation plus endocrine therapy as for postmenopausal women. In premenopausal women who received a prior endocrine therapy within 12 months, the preferred therapy involves ovarian ablation or suppression + endocrine therapy - such as aromatase inhibitors (AIs) - as for post-menopausal patients. (NCCN Breast Cancer Guidelines, version 2.2017).

Based on the clinical benefit shown in postmenopausal patients, AIs in combination with ovarian function suppression (OFS) have been investigated in premenopausal patients with

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breast cancer in neoadjuvant, adjuvant and advanced settings. Results from the randomized phase III trials SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and EXemestane Trial) showed that adjuvant treatment with exemestane+OFS as compared with tamoxifen+OFS, significantly reduced recurrence in premenopausal women with HR+ early breast cancer. Results from both trials (N=5,738) showed statistically significant differences in disease free survival (DFS) at 5 years (91.1% in exemestane + OFS vs 87.3% in tamoxifen + OFS) and rate of freedom from breast cancer at 5 years (92.8% in exemestane+OFS vs 88.8% in tamoxifen+OFS) (Pagani 2014). Studies exploring the combination of third generation AIs and goserelin in metastatic premenopausal BC patients are shown below in Table 1-1. (Montagna 2013)

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

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

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

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

Male breast cancer is rare, with less than 1% of all breast carcinomas occurring in men (Giordano 2005). The pathology is similar to that of female breast cancer, and infiltrating ductal cancer is the most common tumor type. Male breast cancers have high rates of hormone-receptor expression, with approximately 90% of male breast cancers expressing estrogen receptor, and 81% expressing progesterone receptor.

In general, the approach to the treatment of metastatic breast cancer is similar in male and female patients with breast cancer, with hormonal therapy being the often the first approach. Although, historically, surgical ablative therapies such as orchiectomy, adrenalectomy, and hypophysectomy have been used effectively to control metastatic breast cancer in male patients, these surgical procedures are rarely used today and have been supplanted by additive hormonal therapies. Tamoxifen has established efficacy in metastatic male breast cancer, with an

[redacted]

approximate 50% response rate, and is considered an acceptable treatment option. Luteinizing hormone–releasing hormone agonists, with or without antiandrogens, have also been reported to be effective in male breast cancer. There have been case reports of responses to a wide variety of hormonal therapies including progestins, androgens, steroids, aminoglutethamide, estrogens, and letrozole.

Since the hormonal environment in male patients differs from that observed in female patients, the role of AIs in male patients may be different (Doyen J 2010). In men, 80% of circulating estrogens are derived from peripheral aromatization of testicular and adrenal androgens, with direct production from the testes accounting for the remaining 20%. Studies in men patients had demonstrated that non-steroidal AIs lead to a decrease in plasma E2 levels, but these levels can still be detectable in some patients, potentially because of the baseline levels of peripheral androgens (with are subtracts for aromatization) and the testicular production of estrogens, which is not inhibited by NSAIs. Additionally, the use of NSAIs can be associated with feedback loop leading to increase of LH and FSH, which can lead of additional production of androgens, with increased availability of subtracts for aromatization. All these elements converge to a suboptimal suppression of estrogen production in male patients submitted to treatment with monotherapy AI, and create a rational for the combined use of these agents together with LHRH.

The use of aromatase inhibitors together with LHRH was studied as first- or second-line therapy for male patients with HR+ metastatic breast cancer (Giordano SH 2005); 19 patients were evaluated with promising results: 2 patients (10.5 %) had complete response, 7 patients (36.8 %) experienced a partial response, 7 patients (36.8 %) had stable disease lasting ≥6 months, and 3 patients (15.8 %) had progressive disease. Overall, the disease control rate was 84.2 %. Median progression-free survival was 12.5 months (95 % CI 8.2–16.9), median overall survival was 35.8 months (95 % CI 24.4–49.2), 1- and 2-year survival rates were 89.5 and 67 %, respectively. Safety profile was expected and manageable, with no grade 3/4 adverse events

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

1.2.1 Overview of Ribociclib

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

1.2.1.1 Non-clinical data

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

Cardiac safety studies *in vivo* demonstrated QT prolongation with the potential to induce premature ventricular contractions (PVCs) at higher exposure levels. The effects of ribociclib on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), the kidney (concurrent degeneration and regeneration of tubular epithelial

[redacted]

cells), skin (atrophy), bone (decreased bone formation) and testes (atrophy) are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition. The hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) was identified as an additional target organs of toxicity that are not likely related to the primary pharmacology of ribociclib. Generally, all these effects of ribociclib demonstrated either reversibility or a clear trend towards reversibility. Ribociclib did not show an indication for a genotoxic potential. Reproductive studies in animals have demonstrated that ribociclib is embryotoxic, fetotoxic and teratogenic.

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

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

Refer to the most recent ribociclib [Investigator's Brochure] for additional details.

1.2.1.2 Clinical experience

Ribociclib is currently being investigated in patients with breast cancer and other solid tumors in multiple clinical trials at different phases of development. Refer to the most recent ribociclib [Investigator's Brochure] for details on clinical studies with ribociclib.

1.2.1.2.1 Clinical safety of ribociclib

Clinical safety of ribociclib with endocrine agents such as letrozole, tamoxifen, exemestane and fulvestrant has been evaluated in several phase I and III combination trials. The recommended dose of ribociclib in combination with these agents was declared as 600 mg qd on a 3 weeks on/1 week off schedule.

The safety profile of ribociclib in combination with letrozole was investigated in a randomized clinical trial of ribociclib and letrozole versus placebo and letrozole (CLEE011A2301) in 668 treatment-naive postmenopausal women with HR-positive, HER2-negative, advanced BC. Most common treatment-emergent AEs reported in the ribociclib arm in this study occurring in >30% of patients were neutropenia (74.3%), nausea (51.5%), infections (50.3%), fatigue (36.5%), diarrhea (35.0%), alopecia (33.2%) and leukopenia (32.9%). The most common grade 3 or 4 AEs reported in ≥5 % of patients in the ribociclib arm were neutropenia (59.3%), leukopenia (21.6%), hypertension (9.9%), increased alanine aminotransferase (9.3%), lymphopenia (6.9%) and increased aspartate aminotransferase (5.7%). Febrile neutropenia occurred in 1.5% of the patients in the ribociclib arm. Blood creatinine increases were reported in 6.9% of patients. Four patients (1.2%) met the biochemical and clinical criteria for Hy's Law with 3 reported as treatment-related and all 4 returning to normal values after treatment

[redacted]

discontinuation. Eleven patients (3.3%) presented on treatment QTcF prolongation >480 msec. Serious AEs were reported in 21.3% of patients in the ribociclib arm with 7.5% of serious AEs deemed by investigators as treatment-related. There were 3 fatal events in the ribociclib arm (disease progression, sudden death, unknown cause) with 1 AE (sudden death) reported as treatment-related in a patient that had grade 3 hypokalemia and grade 2 QTcF prolongation (483 msec). Neutropenia, QT interval prolongation and hepatobiliary toxicity are considered to be important identified risks for ribociclib which appear to be manageable and reversible with adequate monitoring, interruption and/or reduction of ribociclib dosing.

For a comprehensive review of safety profile of ribociclib in combination with endocrine agents refer to the most recent ribociclib [Investigator's Brochure].

1.2.1.2.2 Clinical efficacy with ribociclib

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

An update to this study with an additional 11 months of follow-up reported a consistent improvement in PFS in comparison with the interim analysis. Median PFS was prolonged by 9.3 mo, from 16.0 mo (95% CI: 13.4–18.2) in the placebo + letrozole arm to 25.3 mo (95% CI: 23.0–30.3) in the ribociclib + letrozole arm (hazard ratio 0.568, 95% CI: 0.457-0.704, p=0.0000000963). 24-mo PFS rates were 54.7% vs 35.9%. The investigator-reported overall response rate was 42.5% (95% CI: 37.2%-47.8%) in the ribociclib arm and 28.7% (95% CI: 23.9%-33.6%) in the placebo arm (in the full analysis set); and 54.5% (95% CI: 48.4%, 60.6.%) and 38.8% (95% CI: 32.7%, 44.9%) in patients with measurable disease at baseline (Hortobyagi et al, ASCO 2017).

Refer to the most recent ribociclib [Investigator's Brochure] for additional details on efficacy profile of ribociclib.

1.2.1.2.3 Clinical Pharmacokinetics of ribociclib

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

[redacted]

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

Concomitant use of ribociclib with strong CYP3A4 inhibitors or strong CYP3A4 inducers should be avoided as ribociclib exposure may be markedly affected. Co-administration of a strong CYP3A4 inhibitor [redacted] increased ribociclib AUC by 3.2-fold following a single oral dose of 400 mg ribociclib ([CLEE011A2101]). Co-administration of a strong CYP3A4 inducer [redacted] decreased ribociclib AUCinf by 89% following a single oral dose of 600 mg ribociclib ([CLEE011A2101]).

Ribociclib is a moderate to strong inhibitor of CYP3A4, but did not have a substantial effect on CYP1A2 substrates in humans ([CLEE011A2106]). Co-administration of [redacted] (CYP3A4 substrate) with multiple doses of ribociclib (400 mg) increased [redacted] exposure by 3.8-fold. Co-administration of [redacted] (CYP1A2 substrate) with multiple doses of ribociclib (400 mg) increased [redacted] 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 DDIs.

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

Refer to the most recent ribociclib [Investigator's Brochure] for additional details.

1.2.2 Overview of Letrozole

Letrozole (Femara®) is a nonsteroidal competitive inhibitor of the aromatase enzyme system with demonstrated efficacy in the treatment of postmenopausal patients with HR+ breast cancer. Letrozole acts by inhibiting in a highly selective fashion the conversion of adrenal androgens to estrogens, which is the primary source of estrogens in postmenopausal women. Letrozole is a highly selective inhibitor of aromatase that induces a 75% to 95% decrease of estrogen levels after two weeks of treatment using daily doses of 0.1 to 5 mg, with no significant clinical and laboratory toxicities nor changes in levels of other hormones of the endocrine system as shown in early phase I (Lipton 1995; Trunet 1996). It is indicated for the adjuvant treatment of women with HR+ early breast cancer as well as the extended adjuvant treatment of patients who have received 5 years of tamoxifen therapy. It is also indicated for the treatment of advanced HR+ breast cancer, both in the first-line setting as well as in patients who have disease progression following anti-estrogen therapy. Letrozole was compared with tamoxifen in a phase III trial in the first line setting in ER+/HER2+ breast cancer. Letrozole was superior to tamoxifen for time to progression (median, 9.4 v. 6.0 months) and median OS trended superior for letrozole (median, 34 versus 30 months) but this difference was not statistically significant (Mouridsen

[redacted]

2001). Trials recently reported - where single-agent letrozole was studied as control arm - demonstrated a median PFS with this agent in 1st line ranging from 14.4 to 15.6 months (Dickler et al 2016; Martin et al 2015; Finn et al 2016).

Letrozole is administered orally once daily at a dose of 2.5 mg and is rapidly and completely absorbed from the gastrointestinal tract. Concomitant intake of food has no effect on the extent of letrozole absorption and only a minor effect on the rate of absorption, which is considered to be of no clinical relevance. The terminal elimination half-life of letrozole is 2 days and steady-state plasma concentration with daily dosing at the standard dose is reached in 2-3 weeks. Letrozole is metabolized via CYP3A4 to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. In addition, CYP2A6 forms the carbinol metabolite as well as its ketone analog [Femara® Prescribing Information, Novartis].

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

1.2.3 Low potential for interaction between ribociclib and letrozole

Letrozole is not expected to affect the metabolism of ribociclib, which is mainly metabolized by CYP3A4 with a 15-26% contribution by the polymorphic enzyme FMO3 (flavin-containing monooxygenase 3) based on in vitro data. Letrozole inhibits CYP2A6 (Ki = 4.6 µM) and CYP2C19 (Ki = 42 µM) in vitro [Jeong 2009; Femara® Prescribing Information], but is not an inhibitor of CYP3A4 or FMO3 and is therefore not expected to affect ribociclib metabolism.

Ribociclib may increase the exposure of co-medications that are substrates of CYP3A4 due to time-dependent inhibition of this enzyme. In vitro studies indicate ribociclib is a reversible inhibitor of CYP3A4 [redacted] and a time-dependent inhibitor of CYP3A4 [redacted]. Letrozole is metabolized via CYP3A4 and CYP2A6 [Femara® Prescribing Information] and hence letrozole concentrations could be affected by coadministration with ribociclib. Preliminary PK data for the combination of ribociclib (600 mg) and letrozole (2.5 mg) indicate ribociclib and letrozole exposures are within the range of values for the respective single agent and the combination is safe and tolerable (see Section 1.2.4).

1.2.4 Overview of LHRH agonists

Luteinizing Hormone-Releasing Hormone (LHRH) or Gonadotropin Releasing Hormone (GnRH) agonists are synthetic analogues of gonadotropin-releasing hormone that by continuous stimulation of the GnRH receptor achieve desensitization of the pituitary gland to LHRH. LHRH agonists differ from the naturally-occurring LHRH by modification(-s) 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. LHRH agonists allowed for use in this study are goserelin or leuprolide. One-month depot formulation of LHRH agonists must be used to

[redacted]

suppress ovarian function in premenopausal women in this study as the 3-month depot formulations do not reliably suppress estrogen levels in all patients (Gradishar et al 2016).

The most common AEs occurring of women treated with LHRH agonists included hot flushes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea and peripheral edema.

The most common AE occurring of men treated with LHRH agonists include a transitory elevation in testosterone levels can occur in men after the first few doses, followed by the expected decrease of these hormonal levels; as a result, the most commonly observed adverse reactions, which occurred in at least 1 out of every 10 men (10%) who participated in clinical trials, are hot flashes, sexual dysfunction, decreased erections and lower urinary tract symptoms (for example, urinary urgency, cystitis, blood in your urine). Some patients may experience a temporary increase in bone pain.

Refer to the most recent regional prescribing information and/or clinical guidelines for more information on LHRH agonists.

2 Rationale

2.1 Study rationale and purpose

Approximately 75% of breast cancers express estrogen receptor (ER) and/or progesterone receptor (PgR) and are dependent of estrogen for growth. Studies of ER+ breast cancer cell lines indicate that estrogens and antiestrogens act in early to mid-G1 phase, via cyclin D1 expression. G1/S transition is under the control of CDKs, particularly CDK4, CDK6 and CDK2. CDK4 and CDK6 are activated by binding to D-type cyclins and act early in G1 phase. The interplay between the ER pathway and the cell cycle control machinery – particularly the control of G1-S transition mediated by cyclin d and CDK 4/6 – provides a strong rational for the combined use of interventions designed to control both nodes as a way to stop the HR+ breast cancer proliferation. This mechanistic approach is corroborated by preclinical evidence of synergistic activity of CDK inhibitors and hormonal agents against HR+ breast cancer in cell lines and animal models and also clinical superiority with the combination (CDKi + hormonal agents) vs. endocrine therapy alone in recent phase II/III trials (PALOMA-1/2/3 with palbociclib; MONALEESA-2 with ribociclib).

Ribociclib (LEE011) is an oral selective inhibitor of CDK 4/6 which has demonstrated activity in HR+BC cell lines in combination with multiple hormonal partners, as well as in clinical studies. While studies in combination with fulvestrant (MONALEESA-3) and NSAI/tamoxifen in premenopausal patients (MONALEESA-7) are ongoing, the phase III trial MONALEESA-2 (ribociclib + letrozole vs. letrozole) was declared as a positive study in an interim assessment, with clinically and statistically meaningful benefit observed with the combination (ribociclib + letrozole) vs letrozole monotherapy in major endpoints (PFS and tumor response); the combination treatment had demonstrated a manageable safety profile based on dose interruptions and/or reductions. These results reinforce the activity of this combination for the treatment of HR+ advanced breast cancer. This trial will support the first authorization granted in the United States (US).

[redacted]

The purpose of this study is to further evaluate the overall safety and tolerability and clinical efficacy of ribociclib in combination with letrozole in a large cohort of patients with HR+, HER2- aBC who have not received prior hormonal treatment for advanced disease.

This study will collect additional safety, tolerability, and efficacy data in a larger and broader patient population including certain clinical situations not included in the phase III trials (e.g., patients treated with prior chemotherapy for advanced disease, ECOG PS 2.) Premenopausal patients with appropriate ovarian suppression achieved with the use of goserelin, will be included in this trial, since the treatment of these patients is quite similar to what postmenopausal women typically receive. In this trial, perimenopausal patients can be included (see Section 5 for definition) and should be treated with goserelin as premenopausal patients. The results from the phase III PALOMA-3 trial with palbociclib + fulvestrant had demonstrated similar superior efficacy vs. fulvestrant monotherapy in both premenopausal (+goserelin) and post-menopausal patients (premenopausal, N=72; median Progression Free Survival (mPFS): 9.5 months (95% CI: 7.4-NE); post-menopausal, N=275; mPFS: 9.9 months (95% CI 8.5-11.0) (Cristofanilli, Lancet Oncology 2016). The trial will also include males with HR+, HER2- aBC, which will generate data about the use of this combination in a very rare patient population with the rational to explore the activity of letrozole + LHRH agonists (as hormonal suppressant) together with ribociclib, given the observed benefit of CDKi when added to standard hormonal therapy in women with HR+ advanced breast cancer.

The results from this trial will provide a relevant set of information to the medical community about the activity of ribociclib + letrozole in HR+ aBC and potentially generate additional hypothesis to be explored in future trials.

2.2 Rationale for the study design

This is an open-label, single arm, multi-center Phase IIIb study to evaluate the overall safety and tolerability and clinical efficacy of ribociclib in combination with letrozole in men and pre/postmenopausal women with HR+, HER2- advanced breast cancer who have not received prior hormonal treatment for advanced disease.

The study design will allow an adequate characterization of the safety profile of this combination (primary objective); efficacy parameters will also be collected in all patients during study participation, which will provide additional information about the combination activity in a broader patient population with aBC.

2.3 Rationale for dose and regimen selection

The dose (oral administration of 600 mg daily) and regimen (Days 1-21 of a 28 day cycle) of ribociclib was selected for this study, since this dose and regimen were shown to be tolerable and efficacious when combined with ET in clinical trials in patients with HR-positive, HER2-negative advanced BC (see Section 1.2.1).

Data from ribociclib [MONALEESA-2] trial (Hortobagyi 2016) and palbociclib ([PALOMA-1] and [PALOMA-2] studies) demonstrated clinical benefit, when used in combination with the non-steroidal aromatase inhibitor letrozole, significantly prolonging progression free survival in postmenopausal women with HR+, HER2-negative advanced breast cancer when compared with letrozole alone (Finn 2015, Finn 2016, Hortobagyi 2016).

[redacted]

In this study, we propose to use the same approach, combining ribociclib with letrozole (+LHRH agonists to achieve adequate hormonal suppression in men/premenopausal women) in HR+, HER2-negative men and pre/postmenopausal women with advanced breast cancer who have received no prior therapy for advanced disease.

The standard doses of goserelin (3.6 mg subcutaneously every 28 days) and leuprolide (7.5 mg intramuscularly every 28 days) will be used in this study as goserelin or leuprolide are not expected to affect the metabolism of nor be affected by co- administration of other drugs.

2.4 Rationale for choice of comparator drugs

This is a non-comparative study. The purpose of this trial is to further evaluate the overall safety/tolerability and clinical efficacy of ribociclib in combination with letrozole in a more diverse population in comparison with the existing phase III study with this combination. Given the positive results from MONALEESA-2 (and also available data with other CDK 4/6 inhibitors), the combination of ribociclib (a CDK 4/6 inhibitor) + letrozole demonstrated superior efficacy in comparison with monotherapy with letrozole, and this treatment is now an accepted standard of care for the treatment of HR+ aBC.

For this reason, the trial is designed as a single-arm, non-comparative study to allow all patients on the study to be treated with this regimen while relevant information about its safety and efficacy will be collected and analyzed.

2.5 Risks and benefits

The treatment landscape in HR+, HER2- aBC has evolved during recent years, with the characterization that CDK 4/6 inhibitors may play an important role in controlling the disease and prolonging PFS in comparison to NSAI alone. Many treatment guidelines have already incorporated CDKi as a treatment choice and palbociclib (the first commercially available CDKi) is already approved in many countries around the world. On March 13, 2017 , the US Food and Drug Administration approved Kisqali® (ribociclib), a cyclin-dependent kinase 4/6 inhibitor, in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Ribociclib, a selective CDK 4/6 inhibitor, has been evaluated in patients with HR+ HER2- aBC, supported by strong preclinical data showing activity against HR+ luminal breast cancer cell lines and synergistic activity with hormonal agents in preclinical models. Study [CLEE011X2107] was the first one to demonstrate activity of ribociclib in combination with letrozole in aBC patients that were treatment-naïve for their advanced disease, with adequate tumor control based on ORR and CBR. Treatment was generally well-tolerated and emerging toxicities were appropriately managed with dose reductions/interruptions. The pivotal phase III trial ([MONALEESA-2]) comparing ribociclib + letrozole with letrozole in a similar patient population as [CLEE011X2107] was declared positive in a preplanned interim analysis with clinically and statistically meaningful benefit observed with the combination (ribociclib + letrozole) vs letrozole monotherapy in major endpoints (PFS and tumor response); the combination treatment had demonstrated a manageable safety profile based on dose interruptions and/or reductions.

[redacted]

This proposed trial is intended to expand the available information about ribociclib in HR+, HER2- aBC either in terms of safety as well as efficacy. The population to be included in this trial is slightly broader than those included in the pivotal phase III trials (e.g. PS 0-2, prior treatment with chemotherapy for advanced disease, premenopausal women and men), which will allow the generation of data in a larger patient population in comparison with other Phase III trials.

Patients included in this trial will potentially benefit from an effective treatment, based on the results from phase I and phase III trials; since all patients included in this trial will receive the combination of ribociclib + letrozole, no ethical issues are expected from this perspective. Patients will continue to receive treatment until disease progression, death, unacceptable toxicity, physician's decision, subject/guardian's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical problems or until 18 months after LPFV in the Core Phase, whichever event occurs first. Patients may be transitioned to the Extension Phase and continue to receive the drugs until progression, intolerance, death or physician/patient decision.

Ribociclib + letrozole treatment is associated with potential AEs, including reversible cytopenias (neutropenia, anemia and thrombocytopenia), GI toxicities (nausea, vomiting, and diarrhea), fatigue, alopecia, elevation in liver enzymes and QT prolongation; some of them can be serious. These toxicities can be managed with appropriate monitoring, dose reductions/interruptions and symptom-related treatments. These risks can be appropriately mitigated in this protocol with clear guidance about eligibility criteria, monitoring of potential toxicities and strategies for therapy management (including instructions related to dose adjustments/interruptions).

The addition of goserelin or leuprolide to premenopausal women / male patients is not expected to affect the metabolism of nor be affected by co-administration of the other drugs (ribociclib and letrozole), so no additional safety risks are expected with this combination.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate the safety and tolerability of ribociclib + letrozole in men and pre / postmenopausal women with HR+, HER2- aBC who received no prior hormonal therapy for advanced disease Note: Throughout this document , perimenopausal and premenopausal status is grouped together and referred as "Premenopausal"	• AEs, Grade 3/4 AEs & SAEs during treatment with ribociclib + letrozole	Refer to Section 10.4
Secondary		
To assess the clinical efficacy and patient reported outcomes of ribociclib + letrozole in the patient population as described above	• Time-to-Progression (TTP) (RECIST 1.1), based on investigators' assessment • Overall response rate (ORR) as defined by RECIST 1.1 for patients with measurable disease • Clinical Benefit Rate (CBR) as defined by RECIST 1.1 (including patients with CR, PR, SD, NCRNPD >24 weeks) • Patient Reported Outcome (PRO) using FACT-B questionnaire	Refer to Section 10.5.1
To evaluate long-term safety of ribociclib + letrozole during Extension Phase	• Frequency and severity of AEs & SAEs during Extension Phase	
To evaluate clinical benefit of ribociclib + letrozole as assessed by investigator during Extension Phase	• Proportion of patients with clinical benefit as assessed by investigator during Extension Phase	

[redacted]

4 Study design

4.1 Description of study design

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

The study will be composed of 2 phases:

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

Approximately 3,000 patients across a diverse number of sites, countries, and regions are expected to be enrolled in this trial. Study treatment of the Core Phase will be provided until disease progression, death, unacceptable toxicities, physician's decision, subject/guardian's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical problems or until 18 months after LPFV, whichever event occurs first (See Figure 4-1).

Enrollment in this trial is not competitive, with the purpose to include a diverse patient population in terms of sites, countries and regions. Each participating country will be assigned a predefined number of patients (based on number of participating sites and available patient population); once this number is achieved, countries may stop enrollment while the study will continue to enroll in other countries/regions. Safety data collected will include all AEs and SAEs including grade 3/4 AEs, events of special interest (Neutropenia including febrile neutropenia, QT prolongation, hepatobililary toxicity), AEs leading to permanent treatment discontinuation or death, vital signs, physical examination, variation of the ECOG performance status, and selected hematology/chemistry parameters at study visits while the patient remains on study and for 30 days after discontinuation.

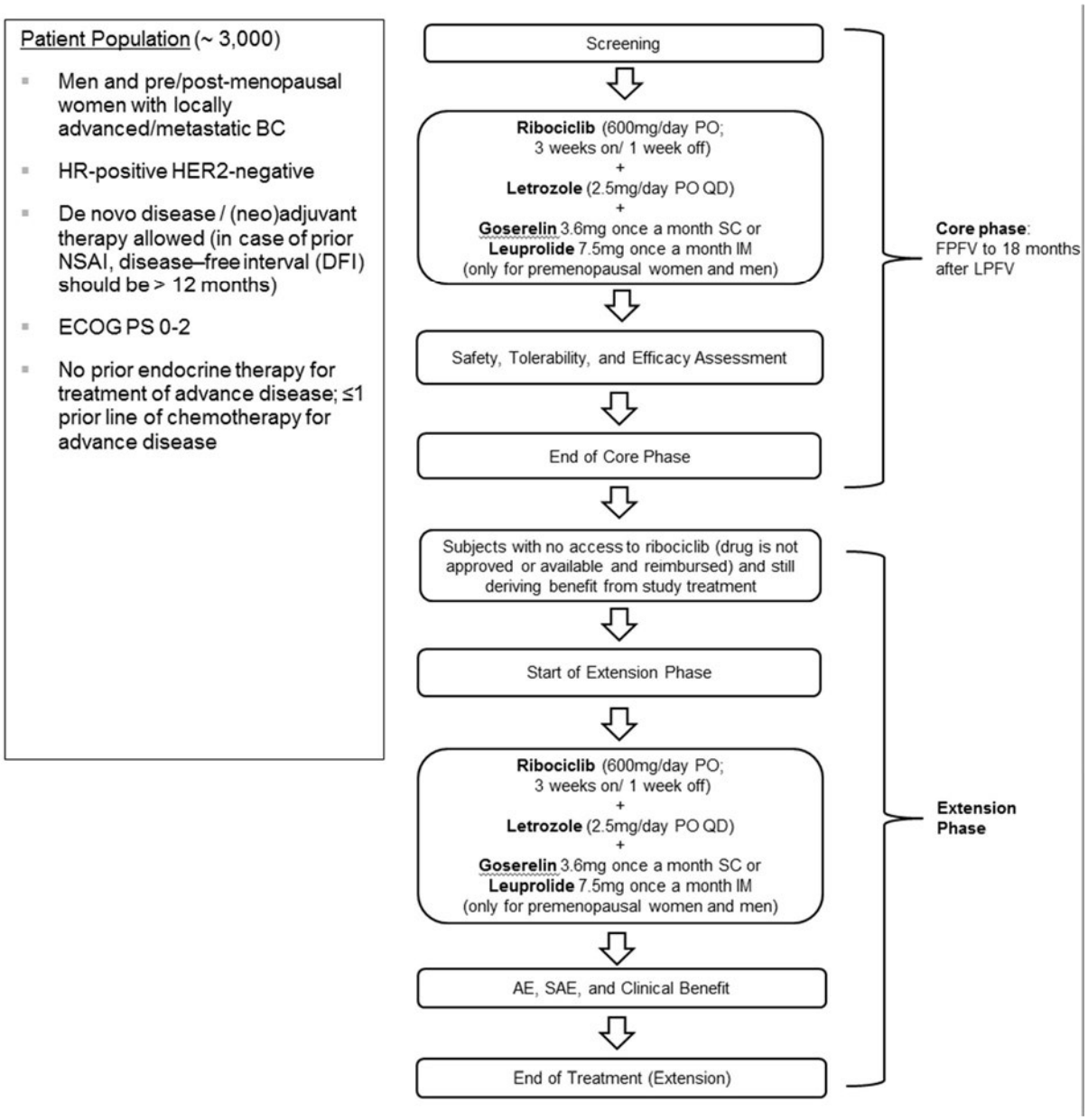
Time to Tumor Progression (TTP) and overall tumor response (ORR/CBR) will be assessed by the investigator using RECIST v1.1 criteria. **Tumor assessments should be performed every 12 weeks (recommended timeframe) or according to the current standard of care (as per local requirements) during treatment phase and at end of treatment (EOT).** It is strongly recommended that a tumor assessment is performed before the patient is switched to a new antineoplastic therapy.

Local/regional sub-studies/analysis can be conducted in the patient population enrolled in [CLEE011A2404] (CompLEEment-1) study. These sub-studies can be designed to explore additional aspects of ribociclib treatment in HR+HER2- advanced breast cancer, which are not

[redacted]

assessed in the current CLEE011A2404 protocol. Examples of sub-studies include biomarker analysis (correlative science studies), additional patient-reported outcome (PRO) evaluations or any other relevant assessments that are not currently evaluated during CLEE011A2404 study. Sub-study protocols must follow the current Novartis process for review and approval of sponsored clinical trials, and should be reviewed and approved by the relevant regulatory authorities and Ethics Committees before implementation.

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

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

4.3 Definition of end of study

Study recruitment will stop when approximately 3,000 patients are enrolled.

The planned overall study duration of the Core Phase will be from FPFV to 18 months after LPFV. At the time of Core Phase end if patients are still deriving clinical benefit and ribociclib is not approved or available and reimbursed, patients may be transitioned to the Extension Phase trial period and continue to receive the drugs until progression, intolerance, death or physician/patient decision, but only safety and clinical benefit as assessed by investigator will be collected during the Extension Phase.

The duration of the Extension Phase will be 18 months from LPLV of the Core Phase. During the Extension Phase, if ribociclib is approved and reimbursed, patients will be transitioned to prescription or drug access/support program(s) according to local laws and regulations.

The study will end after completion of the Extension Phase and all remaining patients will discontinue from the study. Patients who complete the Extension Phase, and continue to derive clinical benefit from the treatment based on the investigator's evaluation will receive ribociclib from prescription (if approved and reimbursed), another Post-Trial Access (PTA) program, or other drug access/support program(s).

Post-Trial Access (PTA) means the provision of treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: patient no longer derives clinical benefit, investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

The mechanism of PTA for this Extension Phase is provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

This PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PSDS for this trial, Novartis will work with investigators to transition patients onto locally available alternative treatment, or standard of care.

The expected median follow-up at the time of study completion will be around 24 months, which is sufficient to provide adequate information about the safety and efficacy of ribociclib + letrozole in the population under investigation. According to data from Study CLEE011A2301 (MONALEESA-2), Grade 3/4 (G3/4) AE of special interest (neutropenia, QT prolongation and liver enzyme elevations) were observed during the first cycles of treatment (QTc prolongation observed during the first 2 cycles; 83.8% of the LFT elevations had been observed during the first 6 cycles; 85% of the G3/4 neutropenia events were observed during the first 12 months of treatment), so a minimal period of 18 months of follow-up seems sufficient to capture these events as part of the primary endpoint of the study. Additionally,

[redacted]

patients entering in the Extension Phase will continue to have safety/tolerability monitored, which will generate relevant data about the long-term safety of this regimen.

4.4 Early study termination

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 subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

5 Population

5.1 Patient population

This trial will be conducted in men and pre/postmenopausal women with HR+, HER2- aBC who have not received any prior hormonal agent for the treatment of advanced disease.

Approximately 3,000 patients are expected to be enrolled in this trial.

Patients enrolled in this protocol are not permitted to participate in additional parallel investigational drug(s) studies while on treatment.

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.

5.2 Inclusion criteria

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

1. Patient is an adult, male or female ≥ 18 years old at the time of informed consent
2. Male or female advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy.
3. In the case of women, both pre/perimenopausal and postmenopausal patients are allowed to be included in this study; menopausal status is relevant for the requirement of goserelin or leuprolide to be used concomitantly with ribociclib and letrozole.
   a. Postmenopausal status is defined either by:
      1. Prior bilateral oophorectomy

      OR

      2. Age ≥ 60

      OR

[redacted]

3. Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range. If patient is taking tamoxifen or toremifene and age < 60, then FSH and plasma estradiol levels should be in post-menopausal range per local normal range (NCCN Guidelines Version 2.2017).

Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure menopausal status.

b. Premenopausal status is defined as either:
   1. Patient had last menstrual period within the last 12 months,

   OR

   2. If on tamoxifen or toremifene within the past 14 days, plasma estradiol and FSH must be in the premenopausal range per local normal range,

   OR

   3. In case of therapy induced amenorrhea, plasma estradiol and/or FSH must be in the premenopausal range per local normal range.

c. Perimenopausal status is define as neither premenopausal nor postmenopausal

   Note: Throughout this document, perimenopausal and premenopausal status is grouped together and referred as "Premenopausal"

4. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory. A confirmatory biopsy is not required.
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.
6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
7. Patient has adequate bone marrow and organ function as defined by ALL of the following laboratory values (as assessed by local laboratory):
   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
   - Platelets $\geq 100 \times 10^9$/L
   - Hemoglobin ≥ 9.0 g/dL
   - Potassium, sodium, calcium corrected for serum albumin and magnesium within normal limits or corrected to within normal limits with supplements before first dose of the study medication
   - INR ≤ 1.5
   - Serum creatinine < 1.5 mg/dl or creatinine clearance ≥ 50 mL/min
   - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be below $2.5 \times$ ULN. If the patient has liver metastases, ALT and AST should be $< 5 \times$ ULN.
   - 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
8. Patient must have a 12-lead ECG with ALL of the following parameters at screening:
   - QTcF interval at screening < 450 msec (using Fridericia's correction)

[redacted]

- Resting heart rate ≥ 50 bpm

9. Patient must be able to swallow ribociclib and letrozole tablets
10. Patient has signed informed consent obtained before any trial-related activities and according to local guidelines
11. Patients must be able to communicate with the investigator and comply with the requirements of the study procedures

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient has a known hypersensitivity to any of the excipients of ribociclib or letrozole including peanuts and soy
2. Patient who received any CDK4/6 inhibitor
3. Patient who received any prior systemic hormonal therapy for advanced breast cancer; no more than one prior regimen of chemotherapy for the treatment of metastatic disease is permitted

   Note:

   - Patients who received (neo) adjuvant therapy for breast cancer are eligible. If the prior neo (adjuvant) therapy included letrozole or anastrozole the disease free interval must be greater than 12 months from the completion of treatment until study entry.
   - Patients who received ≤ 28 days of letrozole or anastrozole for advanced disease prior to inclusion in this trial are eligible.

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 side effects
6. Patient who has not had resolution of all acute toxic effects of prior anti-cancer therapy to NCI CTCAE version 4.03 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion)
7. Patient who has received extended-field radiotherapy ≤ 4 weeks or limited field radiotheraphy for palliation ≤ 2 weeks prior to start of treatment, and who 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 the investigator's discretion). Patients from whom ≥ 25% (Ellis RE 1961) of the bone marrow has been previously irradiated are also excluded. See Appendix 14.4
8. Patient has a concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
9. Patient with central nervous system (CNS) metastases unless they meet ALL of the following criteria:

   - At least 4 weeks from prior therapy for CNS disease completion (including radiation and/or surgery) to starting the study treatment

[redacted]

- Clinically stable CNS lesions at the time of study treatment initiation and not receiving steroids and/or enzyme-inducing anti-epileptic medications for the management of brain metastases for at least 2 weeks

10. 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)
11. Patient has a known history of HIV infection (testing not mandatory)
12. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.)
13. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including but not limited to any of the following:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
    - 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)
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        1. Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
        2. Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication
        3. Inability to determine the QTcF (Fridericia's correction) interval on screening
    - Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening
14. Patient is currently receiving any of the following medications 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 known strong inducers or inhibitors of CYP3A4/5 (See Appendix 14.1)
    - Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5

[redacted]

15. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
16. Participation in a prior investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longer
17. Pregnant or nursing (lactating) women

    Note: Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 21 days after stopping the study medication.

    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 (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male partner sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

    Note: Use of oral (estrogen and progesterone), transdermal, injected, implanted hormone containing intrauterine systems (IUS) or any other hormonal methods of contraception is not allowed in this study

6 Treatment

6.1 Study treatment

For this protocol, the term "investigational drug" refers to the Novartis study drug ribociclib. The other drugs to be used in this study are letrozole and either goserelin or leuprolide (for men / premenopausal women). "Study treatment" in this protocol refers to the combination of drugs and includes investigational drug (ribociclib) as well as letrozole and goserelin or leuprolide (if applicable).

Ribociclib will be supplied by Novartis or its designee as 200 mg tablets as individual patient supply packaged bottles. Letrozole (Femara or generic equivalent), goserelin and leuprolide will be procured locally by Country Pharma Organization or local institution as it is commercially available in each participating country according to local practices and regulations. Storage conditions are described in the medication label. 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 in the eCRF.

[redacted]

6.1.1 Dosing regimen

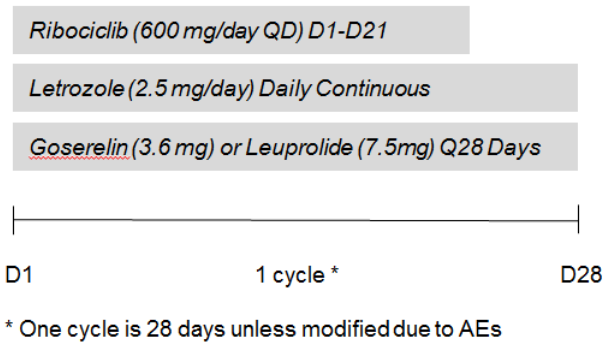
Ribociclib (LEE011) will be given orally once a day on days 1-21 of each 28- day cycle. On days 22-28 ribociclib will not be given ("rest days"). Letrozole will be given orally as per SmPC once a day on a continuous daily schedule (days 1-28 of each 28- day cycle). There will be no "rest" in the letrozole schedule. For men and premenopausal women, either goserelin will be given as an injectable subcutaneous implant or leuprolide will be given as an intramuscular injection. Either goserelin or leuprolide is recommended to be administered on day 1 starting at Cycle 1 and then every 28 days. Goserelin or leuprolide must be given as the monthly injection dosage form, as the 3-month depot dosage forms do not reliably suppress hormonal levels in all patients (NCCN ver. 2 2017). If a patient is already receiving goserelin or leuprolide before C1D1, a 28 days schedule should be maintained based on the pre-existing dosing schedule.

See Table 6-1 and Figure 6-1 for details.

Table 6-1 Dose and treatment schedule

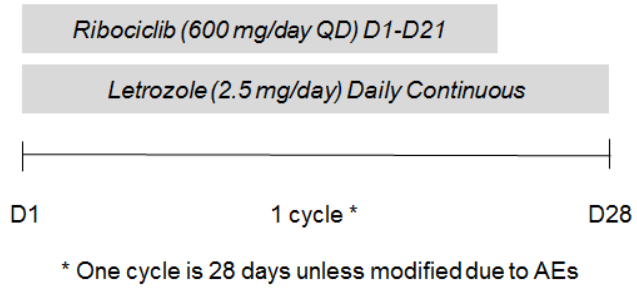
Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Ribociclib	Tablet for oral use	600 mg (3 tablets of 200 mg)	Daily on D1-D21 (28 day cycles)
Letrozole	Tablet for oral use	2.5mg	Continuous Daily
Goserelin	Injectable Subcutaneous implant	3.6 mg	Every 28 days (only for men and premenopausal women)
Leuprolide	Injectable Intramuscular Depot	7.5 mg	Every 28 days (only for men and premenopausal women)

Figure 6-1 Men / Premenopausal regimen



[redacted]

Figure 6-2 Postmenopausal regimen



The study treatment will be administered as a flat-fixed dose (Starting doses: Ribociclib 600 mg QD 3 weeks on/1 week off; letrozole 2.5 mg QD continuously), and not by body weight or body surface area.

The investigator or responsible site personnel should instruct the patient to take the study treatment as per protocol (emphasizing the importance of compliance). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study treatment to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study treatment is provided at each visit.

6.1.1.1 Ribociclib and Letrozole Dosing

Ribociclib and letrozole should be taken as follows:

- Ribociclib is dosed for the first 21 days out of the 28- day cycle.
- Patients should be instructed to take the study treatment combination of ribociclib and letrozole together with a large glass of water (~250 mL or ~8 oz) at the same time each day. Evening doses are strongly not recommended.
- Ribociclib and letrozole can be administered with or without food.
- Patients should be instructed to swallow the ribociclib and letrozole tablets whole and not chew, crush or open them.
- For men and premenopausal women, either goserelin or leuprolide must be administered by injection every 28 days in accordance with the local prescribing information.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medication, due to potential CYP3A4 interaction with the study medications. These foods are known as CYP3A4 inhibitors and have a potential to increase exposure to ribociclib.

[redacted]

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. If the potential for interactions are unknown, then the herbal / dietary supplements should be avoided. (See Appendix 14.1)

6.1.2 Ancillary treatments

Not Applicable.

6.1.3 Rescue medication

Not Applicable.

6.1.4 Guidelines for continuation of treatment

Refer to Section 6.3 Dosing Modification for guidelines for continuation of treatment.

6.1.5 Treatment duration

The planned overall study duration of the Core Phase will be from FPFV to 18 months after LPFV.

The study treatment during the Core Phase will be provided until disease progression, death, unacceptable toxicities, physician's decision, subject/guardian's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical problems or up to 18 months after LPFV.

At the time of Core Phase end, if patients are still deriving benefit and ribociclib is not approved or available and reimbursed, patients may be transitioned to the Extension Phase and continue to receive the drugs until progression, intolerance, death or physician/patient decision, but only safety and clinical benefit as assessed by investigator will be collected.

6.2 Dose escalation guidelines

Not Applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment. These dose modifications are summarized in Table 6-2, Table 6-3, Table 6-4, Table 6-5, Table 6-6, and Table 6-7. 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 a discontinuation in Table 6-3, Table 6-4, Table 6-5, Table 6-6, and Table 6-7 or listed in Section 7.1.5., treatment must be discontinued. If dosing was interrupted for >28 days due to ribociclib related toxicity, ribociclib must be discontinued.

[redacted]

Dose reductions are not permitted for letrozole, goserelin or leuprolide.

Any changes to ribociclib dose or interruption of the study treatment must be recorded on the Dosage Administration Record eCRF. All patients will be followed for (S)AEs for 30 days following the last dose of ribociclib.

6.3.1.1 Letrozole

The established clinical dose of letrozole (2.5 mg/day) will be used and no dose modification of letrozole is planned in this study. The letrozole SmPC should be consulted regarding full prescribing information, monitoring, and management of adverse events.

In the case where letrozole is required to be permanently discontinued the patient must be discontinued from study.

6.3.1.2 Goserelin and leuprolide

The established clinical dose of goserelin or leuprolide will be used in men and premenopausal women patients and no dose modification is planned in this study. Patients receiving LHRH agonists will be monitored regularly per local institutional clinical guidelines to confirm a post-menopausal status, according to local laboratory ranges of FSH and estradiol levels.

Refer to the most recent regional prescribing information and/or clinical guidelines for more information on LHRH agonists.

6.3.1.3 Ribociclib

Ribociclib should not be used as monotherapy.

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of ribociclib therapy. Refer to Table 6-2 for guidance.

Table 6-2 Ribociclib Dose Modification Guidelines

	Ribociclib	
	Dose	**Number of tablets and strength**
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 tablets

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, and Table 6-7.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. However, for events requiring a discontinuation in Table 6-3, Table 6-4, Table 6-5, Table 6-6, and Table 6-7 or listed in Section 7.1, treatment must be discontinued.

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

[redacted]

6.3.1.3.1 Recommendations on Adjustment of Ribociclib Treatment Cycles in the Case of Dose Interruptions/ Reinitiation

Delayed start of a cycle:

In the case of ribociclib being withheld at Cycle (x) D1 based on investigator's judgement, the patient should reinitiate ribociclib on a 3 week ON/ 1 week OFF schedule once the assessment(s) are within acceptable levels according to Section 6.3 Dose Modifications. The visit schedule should be adjusted based on the ribociclib treatment schedule.

Mid-cycle dose interruption:

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

In the case of ribociclib being withheld for ≥ 7 days during any cycle, patient should reinitiate ribociclib to **a new** 28 calendar day treatment schedule (3 weeks ON/ 1 week OFF) once the assessment(s) are within acceptable levels according to Section 6.3 Dose Modifications. The visit schedule should be adjusted based on the ribociclib treatment schedule.

Table 6-3 Ribociclib dose reduction/interruption and management recommendations for hematological adverse drug 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.

[redacted]

Toxicity/Grade	Dose Adjustment and Management Recommendations
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 reduction/interruption and management recommendation for hepatic toxicities (CTCAE v4.03)

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 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, 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 gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert's Syndrome, other pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert's Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	

[redacted]

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 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 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 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 patient with elevated AST or ALT or total bilirubin at baseline: 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 metastasis, and alcohol intake.	

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

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

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

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 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], , 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: Alkaline Phosphatase (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 ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat Liver Function Tests as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

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

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

- Repeating liver enzyme and serum bilirubin tests **two or three times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases, including history of any pre-existing liver conditions or risk factors.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.

[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.
- Consider a liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury

All cases of DILI confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant", thus meeting the definition of SAE (Section 8.2.1), 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.

6.3.1.3.3 Additional follow-up for QTc prolongation

Table 6-5 Ribociclib dose adjustment and management recommendation for QTcF prolongation

Grade	Dose Modification
For All Grades	1. Check the quality of the ECG and the QT value and repeat if needed. 2. Perform analysis of serum electrolytes (K+, Ca++ correct for albumin, Phos, Mg++). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib.
1 QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustment required.
2 QTcF 481-500 ms	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. Restart ribociclib with dose reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. If QTcF ≥ 481 ms recurs, ribociclib should be reduced again by 1 dose level. Repeat ECG 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." 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. Refer to Table 6-2 for dosing schedule. • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. Repeat ECG 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.

[redacted]

Grade	Dose Modification
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.

6.3.1.3.4 Additional follow-up for Interstitial Lung Disease (ILD)/pneumonitis (CTCAE v4.03)

Table 6-6 Ribociclib dose adjustment and management recommendation for ILD/pneumonitis

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

6.3.1.3.5 Guidance for all other adverse reactions

Consider performing an analysis of serum potassium, calcium, and magnesium for all adverse reactions that are potentially associated with electrolyte imbalance. If electrolyte values are outside of the normal range, interrupt ribociclib administration, correct electrolytes with supplements or appropriate therapy as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

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

Table 6-7 Ribociclib dose reduction/interruption 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.

[redacted]

3	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib dose the next lower dose level. If toxicity recurs at grade 3, discontinue ribociclib.
4	Discontinue ribociclib and treat with appropriate medical therapy.

6.3.2 Follow-up for toxicities

Patients who complete treatment or whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary.

All patients will be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment. Patients stopping study treatment but still receiving ribociclib outside of this trial (e.g., commercial supply) will be followed up for safety up to 30 days independently of resolution/stabilization of AEs. Further reports of AEs after 30 days of EOT should follow local pharmacovigilance practices.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed. Please consult the list of prohibited medications and the list of use with caution medications for further guidance (see Table 14-1 and Table 14-2 in Appendix 14.1).

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Prior and Concomitant Medications or the Surgical and Medical Procedures eCRF.

If patients take concomitant medications chronically, any change in the dose or schedule of any concomitant medication throughout the study period should be clearly documented

6.4.1.1 Bisphosphonates and denosumab

Bisphosphonates and denosumab are generally allowed with the following comments:

- Bisphosphonate/denosumab therapy for the treatment of osteoporosis is permitted.
- Bisphosphonate/denosumab therapy for the prevention of skeletal related events for patients with bone metastases is permitted.
- Chronic concomitant bisphosphonate/denosumab therapy for **the prevention of bone metastasis** is permitted.

[redacted]

Patients taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible.

6.4.1.2 Hematopoietic growth factors

Prophylactic use of WBC growth factors with ribociclib is not recommended.

6.4.1.3 Palliative radiotherapy

Palliative radiation is permitted. It should not be delivered to target lesion. Cumulative courses of RT should not encompass >25% of irradiated bone marrow (see Appendix 14.4).

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

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

6.4.1.4 Use of antiemetic medications

Ribociclib has low to minimal emetogenic potential according to the definition of antineoplastic agent emetogenicity (Grunberg et al 2010). 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, 2017; Roila F 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 Appendix 1 for list of medications that are prohibited or allowed to be used with ribociclib.

6.4.2 Permitted concomitant therapy requiring caution

Medications to be used with caution during combined ribociclib and letrozole (+/- goserelin or leuprolide) in this study are listed below (see Table 14-2 in Appendix 14.1). 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 (Bile Salt Export Pump) (based on *in vitro* data co-administration with ribociclib may lead to intrahepatic cholestasis)
- Medications that carry a possible risk for QT prolongation (may precipitate QT prolongation and TdP)
- Sensitive substrates of the renal transporters, MATE1 and OCT2 (has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements)

[redacted]

- Sensitive substrates of transporter BCRP (has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements)
- Substrates metabolized predominantly by CYP2C19 or CYP2A6 with a narrow therapeutic index (that could be affected by letrozole)

6.4.2.1 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 subtherapeutic levels. Systemic corticosteroid treatment should not be given during the study, 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 ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic)

6.4.3 Prohibited concomitant therapy

The following medications are prohibited during study treatment in the study (see Table 14-1 in Appendix 14.1). This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions:

- Strong inhibitors or inducers of CYP3A4/5 (may significantly increase or decrease ribociclib exposure, respectively)
- Substrates of CYP3A4/5 with a narrow therapeutic index (ribociclib may increase exposure to these medications resulting in toxicity to these medications)
- Medications with a known risk for QT prolongation (may precipitate QT prolongation and TdP in combination with ribociclib)
- Other investigational and antineoplastic therapies
- Herbal preparations/medications 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 all these preparations at least 7 days prior to first dose of study treatment.

6.4.4 Drugs with QT prolongation

As far as possible, avoid co-administering medications with a "Known", "Possible" or "Conditional" risk of TdP (www.crediblemeds.org) or any other medication with the potential to increase the risk of drug-related QT prolongation (e.g. via a potential DDI increasing the exposure of ribociclib or the exposure of the QT prolonging drug). If concomitant administration of drugs with a known risk of TdP is required and cannot be avoided, ribociclib must be interrupted (see Table 6-5). If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk" of TdP is required, based on

[redacted]

the investigator assessment and clinical need, study treatment may be resumed under close clinical and ECG monitoring to ensure patient safety. A list of drugs associated with QT prolongation and/or TdP is available online (www.crediblemeds.org). Medications with a known risk for QT prolongation are prohibited during study treatment.

Refer to the ribociclib [Investigator's Brochure] and letrozole, goserelin, and leuprolide drug package insert in addition to Appendix 14.1 for information on possible interactions with other drugs.

6.5 Patient numbering and treatment assignment

6.5.1 Patient 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 his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT system. If the patient fails to meet eligibility criteria for any reason, the reason will be entered into the Screening Phase Disposition eCRF page. The patient will be entered as screen failure in the IRT system.

Once Subject No. is assigned, it must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened.

6.5.2 Treatment assignment

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be assigned via IRT to treatment. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign the patient to the ribociclib treatment and will specify a unique medication number for the first package of study ribociclib to be dispensed to the patient.

6.5.3 Treatment blinding

Not applicable; this is an open label study.

6.6 Study drug preparation and dispensation

Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive ribociclib on an outpatient basis. The investigator shall provide the patient with instructions for ribociclib administration according to the protocol.

Letrozole, and either goserelin (if applicable) or leuprolide (if applicable) should be dispensed and administered according to the local prescribing information and practice.

[redacted]

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF(s).

6.6.1 Study treatment packaging and labeling

Ribociclib will be provided as global clinical open-labeled supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Letrozole, goserelin and leuprolide will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and labeled in the country when possible.

Study treatment labels (see Table 6-8) will comply with the legal requirements of each country and will include storage conditions, and a unique medication. Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. If the label has 2 parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document (Drug Label Form) for that patient's unique patient number.

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

Table 6-8 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Ribociclib	Tablets in bottles	Labeled as 'LEE011" Study treatment packaging has a 2-part label.
Letrozole	Refer to local product information	Refer to local product information
Goserelin	Refer to local product information	Refer to local product information.
Leuprolide	Refer to local product information	Refer to local product information.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel 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, the study treatments should be stored according to the instructions specified on the drug labels (Table 6-9) and in the [Investigator's Brochure].

Table 6-9 Supply and storage of study treatment

Study treatments	Supply	Storage
Ribociclib	Centrally supplied by Novartis	Refer to study treatment label
Letrozole	Locally	Refer to local product information
Goserelin	Locally	Refer to local product information
Leuprolide	Locally	Refer to local product information

[redacted]

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and 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.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column).

Note:

- During screening visits, lab assessments including white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count, hemoglobin, platelets, INR, ALT, AST, total bilirubin (or direct bilirubin if Gilbert's Syndrome), serum creatinine, electrolytes (potassium, sodium, calcium corrected for serum albumin, and magnesium) are required to be collected within 14 days of C1D1 for eligibility assessment.
- During treatment phase, only selected labs assessments are required to be collected in the clinical database at the patient scheduled visits: WBC, ANC, absolute lymphocyte count,

[redacted]

hemoglobin, platelets, AST, ALT, ALP, total bilirubin, and direct bilirubin (if clinically indicated). Electrolytes should be monitored at the beginning of each cycle before resuming ribociclib dose during the first 6 cycles and as clinically indicated thereafter. The results should not be captured in clinical database. Eventual abnormal electrolyte lab results should be reported as AEs at the investigator's discretion.

- ECG will be performed at screening (within 5 days of C1D1), C1D15, C2D1, then as clinically indicated, and EOT.
- If treatment is withheld at any time during the study, all study visits, safety assessments, and efficacy assessments should be adjusted accordingly to match the treatment cycles.
- For all visits, there is a +/-3 day window on assessments to take into account scheduling over public holidays, if not explicitly specified otherwise.

[redacted]

Table 7-1 Visit evaluation schedule (Core Phase)

	Category	Reference to Protocol Section	Screening Phase	Core Treatment Phase									End of study treatment (EOT) within 7 days from the last dose of study treatment	Safety follow up within 30 days of last dose of study treatment
Visit name			**Screening (-28 Days to Day 1)**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1-C11D1**	**C12D1 and subsequent cycles (up to cycle 36)**		
Screening														
Study Informed Consent	D	7	×											
IRT Screening (after ICF signature)	D	7.1.2	×											
Patient History														
Demography	D	7.1.2	×											
Inclusion / Exclusion criteria	D	5.1	×											
Medical History	D	7.1.2	×											
Diagnosis and extent of cancer	D	7.1.2	×											
Prior antineoplastic therapy-medication	D	7.1.2	×											

[redacted]

	Category	Reference to Protocol Section	Screening Phase	Core Treatment Phase									End of study treatment (EOT) within 7 days from the last dose of study treatment	Safety follow up within 30 days of last dose of study treatment
Visit name			**Screening (-28 Days to Day 1)**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1-C11D1**	**C12D1 and subsequent cycles (up to cycle 36)**		
Prior antineoplastic therapy- radiotherapy	D	7.1.2	x											
Prior antineoplastic therapy- surgery	D	7.1.2	x											
Prior and concomitant medication	D	7.1.2	× Continuous – up to 30 days after last dose											
Surgical and Medical procedures	D	7.1.2	× Continuous – up to 30 days after last dose											
IRT														
Eligibility checklist (within IRT)	S	7.1.2	×											
IRT - ribociclib administration	S	7		×		×		×	×	×	× 2 cycle supply (e.g. 6, 8, 10)	× 3 cycle supply (12, 15, 18…)	×	

[redacted]

	Category	Reference to Protocol Section	Screening Phase	Core Treatment Phase									End of study treatment (EOT) within 7 days from the last dose of study treatment	Safety follow up within 30 days of last dose of study treatment
Visit name			**Screening (-28 Days to Day 1)**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1-C11D1**	**C12D1 and subsequent cycles (up to cycle 36)**		
Physical Examination														
Physical examination	S	7.2.2.1	×	×		×		×	×	×	× Every 2 cycles (6, 8, 10)	× Every 3 cycles (12,15, 18…)	×	
ECOG performance status	D	7.2.2.4	×	×		×		×	×	×	× Every 2 cycles (6, 8,10)	× Every 3 cycles (12, 15, 18...)	×	
Height	D	7.2.2.3	×											
Weight	D	7.2.2.3	×			×			×		× Every 2 cycles (6, 8,10)	× Every 3 cycles (12, 15, 18…)	×	
Vital signs	D	7.2.2.2	×	×		×		×	×	x	× Every 2 cycles (6, 8,10)	× Every 3 cycles (12, 15, 18…)	×	

[redacted]

	Category	Reference to Protocol Section	Screening Phase	Core Treatment Phase									End of study treatment (EOT) within 7 days from the last dose of study treatment	Safety follow up within 30 days of last dose of study treatment
Visit name			**Screening (-28 Days to Day 1)**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1-C11D1**	**C12D1 and subsequent cycles (up to cycle 36)**		
Laboratory assessments (local)														
Hematology (selected parameters: WBC, ANC, lymphocytes, platelets, hemoglobin)	D	7.2.2.5.1	× (-14 Days to Day 1)		×	×	×	×	×	×	× (cycle 6 only), then as clinically indicated)	as clinically indicated	×	
Chemistry (see Table 7-5)	D	7.2.2.5.2	× (-14 Days to day 1)		×	×	×	×	×	×	× (cycle 6 only), then as clinically indicated)	as clinically indicated	×	
Coagulation (see Table 7-5)	D	7.2.2.5.3	×	As clinically indicated									×	
Tumor Assessment														
Tumor Assessment	D	7.2.1	×	Recommendation: every 12 weeks from start of study treatment can be performed at different intervals according to the local standard of care									×	

[redacted]

	Category	Reference to Protocol Section	Screening Phase	Core Treatment Phase									End of study treatment (EOT) within 7 days from the last dose of study treatment	Safety follow up within 30 days of last dose of study treatment
Visit name			**Screening (-28 Days to Day 1)**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1-C11D1**	**C12D1 and subsequent cycles (up to cycle 36)**		
Cardiac Assessment														
ECG (standard 12 lead)	D	7.2.2.6	× (-5 Days to Day 1)		×	×		As clinically indicated					×	
Safety														
Serum Pregnancy test (only premenopausal patients)	D	7.2.2.5.4	x										x	
Urine pregnancy test (only premenopausal patients)	D	7.2.2.5.4		x every cycle										
Adverse events	D	8.1	× Continuous – up to 30 days after last dose of study treatment											
Patient Reported Outcome														
FACT-B (female patients only)	D	7.2.3		×		×		×	×	×	× Every 2 cycles (6, 8, 10)	x Every 3 cycles (12, 15, 18…)	×	

[redacted]

	Category	Reference to Protocol Section	Screening Phase	Core Treatment Phase									End of study treatment (EOT) within 7 days from the last dose of study treatment	Safety follow up within 30 days of last dose of study treatment
Visit name			**Screening (-28 Days to Day 1)**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1-C11D1**	**C12D1 and subsequent cycles (up to cycle 36)**		
Treatment														
Letrozole	D	6		× (Daily)										
Ribociclib	D	6		× (Daily: Day 1-21)										
Goserelin (men /premenopausal women only)	D	6		x		x		x	x	x	x every cycle	x every cycle		
Leuprolide (men /premenopausal women only)	D	6		x		x		x	x	x	x every cycle	x every cycle		
Discontinuation														
Antineoplastic therapies since discontinuation of study treatment	D	7											×	
End of phase disposition	D	7	×										×	

[redacted]

Table 7-2 Visit evaluation schedule (Extension Phase)

	Category	Reference to Protocol Section	Extension Treatment Phase				End of study treatment (EOT) within 7 days from the last dose of study treatment	Safety follow up within 30 days of last dose of study treatment
Visit name			E-C1D1	E-C4D1	E-C7D1	E-C10D1 and subsequent cycles		
Concomitant medication (only if related to (s)AE)	D	7.1.2	X Continuous – up to 30 days after last dose					
Surgical and Medical procedures (only if related to (s)AE)	D	7.1.2	X Continuous – up to 30 days after last dose					
IRT								
IRT – ribociclib administration	S	7	X Every 3 cycles dispense 3 cycle supply (Cycle 1, 4, 7, 10…)					
Safety								
Adverse events	D	8.1	X Continuous – up to 30 days after last dose of study treatment					
Pregnancy Serum Test (only premenopausal patients)	S/D	7.2.2.5.4					X	
Pregnancy urine test (only premenopausal patients)	S/D	7.2.2.5.4	X every cycle					
Confirmation of Clinical Benefit (assessed by investigator)	D	7	X Every 3 cycles (1, 4, 7, 10…)					

[redacted]

	Category	Reference to Protocol Section	Extension Treatment Phase				End of study treatment (EOT) within 7 days from the last dose of study treatment	Safety follow up within 30 days of last dose of study treatment
Visit name			E-C1D1	E-C4D1	E-C7D1	E-C10D1 and subsequent cycles		
Treatment								
Letrozole	D	6	X (Daily)					
Ribociclib	D	6	X (Daily: Day 1-21)					
Goserelin (men/premenopausal only)	D	6	X (Monthly)					
Leuprolide (men/premenopausal only)	D	6	X (Monthly)					
Discontinuation								
Antineoplastic therapies since discontinuation of study treatment	D	7					X	
End of phase disposition	D	7					X	

[redacted]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

After signing the study ICF, the screening assessments will be done within 1 to 28 days prior to start of study treatment or within 5 days of start of study treatment for selected assessments (i.e., ECG; see Table 7-1 for list of assessments to be performed).

Note: **Any screening assessment that is done outside the screening window** (Day -28 to Day 1 or Day -5 to Day 1 for ECG assessment as applicable) **must be repeated prior to C1D1**.

If patient meets all inclusion and no exclusion criteria, the screening labs can be used for baseline if patient is dosed within 14 days of the screening visit. If patient cannot be dosed within 14 days of screening, then the labs should be repeated the day before patient starts dosing (see baseline visit in Table 7-1)

Any blood work already completed during the regular work-up of the patient within 5 calendar days before signing the main study ICF can be considered as the screening assessments for this study. Tests not considered standard practice should only be performed after the patient has signed ICF.

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 assignment). In this case the Subject No. assigned to the patient initially will be used and the patient will be identified with this number throughout his/her entire participation to the study.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. 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.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of study treatment, including before signing the main study ICF can be considered as the baseline images for this study.

7.1.2.1 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.

[redacted]

7.1.2.2 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 following eCRF pages will be collected on screen failures:

- Demographic information
- Informed consent
- Inclusion/Exclusion
- Death
- Withdrawal of consent, if applicable, must also be completed. 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 Section 8 for SAE reporting details). If the patient fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the patient was not enrolled.

7.1.2.3 Patient demographics and other baseline characteristics

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

- Demography (Date of birth and initials (where permitted), sex, race, ethnicity)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade.
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications taken within 30 days before the first dose is administered must be recorded on the Prior and Concomitant medication eCRF page and updated on a continual basis if there are any new changes to the medications.
- Surgeries and Medical Procedures prior to Informed Consent are recorded on the Medical History eCRF. The Surgical and Medical Procedures after signing Informed Consent are recorded on Surgical and Medical Procedures eCRF.
- Patient-reported outcome Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire (See Section 7.2.3).

Furthermore the following assessments will be performed:

- Vital signs
- Height, weight
- Physical examination
- Performance status (ECOG)

[redacted]

- Laboratory evaluations (hematology, INR, chemistry)
- ECG
- Radiological assessments (e.g. CT Scan)

7.1.3 Run-in period

Not Applicable.

7.1.4 Treatment period

Core Phase

Patients will be treated with ribociclib + letrozole (goserelin or leuprolide will be added to this combination in men and premenopausal women) until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason. For details of assessments, refer to Table 7-1.

Extension Phase

Patients will be treated with ribociclib + letrozole (goserelin or leuprolide will be added to this combination in premenopausal patients and men) until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason. For details of assessments, refer to Table 7-2.

7.1.5 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time.

If a patient decides to discontinue from the study treatment (Core or Extension Phase), the investigator must make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

- The investigator may discontinue study treatment (Core or Extension Phase) for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.
- Patients will discontinue from the Core Phase 18 months after LPFV. In the event study patients are still deriving benefit at the end of the Core Phase and ribociclib is not approved or available and reimbursed, patients may be transitioned to the Extension Phase and continue to receive the study treatment until progression, intolerance, death, or physician/patient decision; only safety and clinical benefit as assessed by investigator will be collected.
- During the Extension Phase, if ribociclib is approved and reimbursed, patients will be transitioned to prescription or drug access/support program(s) according to local laws and regulations.
- The study will end after completion of the Extension Phase and all remaining patients will discontinue from the study. Patients who complete this Extension Phase, and continue to derive clinical benefit from the treatment based on the investigator's evaluation will

[redacted]

receive ribociclib from prescription (if approved and reimbursed), another Post-Trial Access (PTA) program, or other drug access/support program(s).

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

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

[redacted]

- Adverse Event
- Lost to follow-up
- Physician decision
- Progressive Disease
- Protocol deviation
- Study terminated by sponsor
- Technical problems

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

- Pregnancy
- Death
- Subject/Guardian decision

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

- Adjustments to study treatment due to toxicity that result in discontinuation. Please refer to Section 6.3
- Use of prohibited medication. Please refer to Section 6.4.3
- Any other protocol deviation that results in a significant risk to the patient's safety.

Patients who discontinue study treatment should undergo an End of Treatment (EOT) visit followed by a 30-day safety follow-up.

At EOT visit, all the assessments as listed in Table 7-1 will be performed. 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 investigator or his/her delegate must also contact the IRT to register the patient's discontinuation from study treatment within 2 days of EOT visit.

7.1.6 Withdrawal of 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

[redacted]

any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

7.1.7 Follow up for safety evaluations

All patients who complete the Core Phase of the study but do not transition to the Extension Phase must have safety evaluations completed within 30 days after the last dose of study treatment (ribociclib + letrozole + either goserelin or leuprolide). Patients who continue to the Extension Phase will complete safety evaluations within 30 days after the last dose of study treatment of the Extension Phase.

Data collected should be added to the Adverse Events eCRF and the Concomitant Medications eCRF.

7.1.8 Lost to follow-up

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

7.2 Assessment types

7.2.1 Efficacy assessments

Efficacy assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.2 (Appendix 14.3) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 7-3. There will be no central review of imaging assessments.

Table 7-3 Imaging Assessment Collection Guidance

Procedure	Screening: day−28 to day 1	Treatment phase*	End of treatment*
CT or MRI (Chest, Abdomen, Pelvis)	Mandated	Recommend every 12 weeks or at different intervals according to local standards of care during treatment phase	Mandated
Brain CT or MRI	Only if suspected brain metastases	As clinically indicated	As clinically indicated
Whole body bone scan**	Mandated	As clinically indicated	As clinically indicated
Bone X-ray, CT or MRI	Only if skeletal abnormalities identified by whole body bone scan (or skeletal survey) at screening, which are not visible in the chest, abdomen, pelvis CT/MRI.	If bone lesion at screening, recommend every 12 weeks or at different intervals according to local standards of care during treatment phase	Mandated only if bone lesion at screening

[redacted]

Procedure	Screening: day−28 to day 1	Treatment phase*	End of treatment*
Skin visual inspection and measurement	Only if skin lesions at screening	Recommend every 12 weeks or at different intervals according to local standards of care during treatment phase	Mandated if skin lesions at screening
CT or MRI of any disease outside of chest, abdomen and pelvis (e.g., neck)	Only if suspected lesion at screening	If lesion identified at baseline, recommend 12 weeks or at different intervals according to local standards of care during treatment phase	Mandated if lesion at screening
*Tumor evaluation at EOT is required for patients who discontinue study treatment before the first scheduled post-baseline tumor assessment (week 12) and for patients whose previous tumor assessment did not demonstrate PD and was done more than 28 days prior to end of treatment visit. ** Whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, sodium fluoride positron emission tomography (NaF PET) or fluorodeoxyglucose (FDG) PET).			

Baseline/Screening imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after study treatment cannot be considered baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain CT or MRI, if clinically indicated
- Whole body bone scan
- Localized bone CT, MRI or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- Skin visual inspection and measurement (only if skin lesions at screening)
- CT or MRI of other metastatic sites (e.g. neck), if clinically indicated

If a patient is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

If brain metastases are suspected at baseline, brain MRI or CT should be completed. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

A whole body bone scan should be performed per institutional standard of care [e.g., Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride (NaF) PET]. Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.

[redacted]

If clinically indicated, CT or MRI of other areas (e.g., neck) of disease as appropriate should be performed.

If skin lesions are present at screening, lesion will be measured and visually monitored.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments as described in Table 7-3 should be performed at the timepoints specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1). Imaging assessments for response evaluation will be performed in recommended timeframe of every 12 weeks or at different intervals according to the local standard of care after screening/baseline, until disease progression, death, lost to follow-up or withdrawal of consent. Imaging assessments should be scheduled using the first dose date as the reference date (not the date of the previous tumor assessment), and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by visual inspection and measurement and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 14.3).

Confirmation of Clinical Benefit

During the Extension Phase, at every 3 months visit the investigator is required to confirm that the patient continues to receive clinical benefit and may continue receiving study treatment.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical exam, vital signs, hematological and chemistry labs as well as collecting of the adverse events at every visit during Core Phase (Table 7-1). For patients who continue study participation during Extension Phase, (S)AEs and related

assessments and, pregnancy test will be performed (Table 7-2). For details on AE collection and reporting, refer to Section 8.

Premenopausal women must complete the following pregnancy tests:

- Screening – Serum pregnancy test done locally
- Every 4 weeks during treatment – urine pregnancy test. Can be administered at patient's home
- End of Treatment visit – serum pregnancy test done locally

Premenopausal women who administer urine pregnancy testing at home should complete a simple diary with the dates and the outcome of the urine pregnancy tests while on study treatment. In case of a positive pregnancy test, the instructions in Section 8.4 should be followed.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information about the physical examination must be present in the source documentation at the study site. Physical examination is to be performed according to the visit schedule as outlined in Table 7-1.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.4 Performance status

ECOG Performance status scale will be used as described in the Table 7-4.

Table 7-4 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

[redacted]

Grade	ECOG status
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

7.2.2.5 Laboratory evaluations

Local site laboratories will be used for the analysis of scheduled hematology, biochemistry, and other blood specimens collected as part of safety monitoring. All unscheduled blood testing will also be performed locally. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require dose adjustments in ribociclib treatment (see Section 8.1) constitute an adverse event (AE) and must be reported as an AE on the AE eCRF page.

Laboratory values obtained at the screening visit will be used to assess eligibility to meet Inclusion criteria. If patient meets all inclusion and no exclusion criteria, the screening labs can be used for baseline if patient is dosed within 14 days of the screening visit. If patient cannot be dosed within 14 days of screening, then the labs should be repeated the day before patient starts dosing (see baseline visit in Table 7-1).

Only selected laboratory parameters (see Table 7-5) will be collected on the eCRF.

Table 7-5 Local Clinical laboratory parameters collection plan

Test Category	Test Name	
Hematology	WBC, ANC, absolute lymphocyte count, hemoglobin, platelets	
Chemistry	Screening	ALT (SGPT), AST (SGOT), calcium corrected for serum albumin, creatinine or creatinine clearance, potassium, sodium, magnesium, total bilirubin (or direct bilirubin if Gilbert's syndrome)
	Scheduled visits	Alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, direct bilirubin (if clinically indicated) Note: potassium, sodium, calcium corrected for serum albumin, and magnesium are to be monitored but are not captured in the eCRF. Abnormal electrolyte lab results should be reported as AEs at the investigator's discretion.
Coagulation	International normalized ratio [INR]	
Pregnancy	Serum and Urine	

7.2.2.5.1 Hematology

Hematology tests are to be performed according to the Visit Evaluation Schedules outlined in Table 7-1. For details of the Hematology panel refer to Table 7-5.

7.2.2.5.2 Clinical chemistry

Chemistry tests are to be performed according to the Visit Evaluation Schedules outlined in Table 7-1. For details of the Chemistry panel refer to Table 7-5.

[redacted]

7.2.2.5.3 Coagulation

INR is to be performed according to the Visit Evaluation Schedules outlined in Table 7-1.

7.2.2.5.4 Pregnancy and Hormonal Levels

Pregnancy tests are to be performed according to the Visit Evaluation Schedules outlined in Table 7-1 and Table 7-2

A positive urine test is required to be confirmed by an immediate serum pregnancy test.A positive pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must be discontinued from the study.

FSH and estradiol will be collected locally and used for screening and confirmation of menopausal status and clinically monitored as indicated. FSH and estradiol results are not recorded in the eCRF.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard 12 lead ECG assessments will be performed locally at screening, C1D15, C2D1, and thereafter as clinically indicated, and EOT visit (see Table 7-1). There will be no central review of ECGs. QT interval corrected by Fridericia's formula (QTcF) will be used in this trial for trial eligibility and safety assessments.

If an abnormal ECG or QTcF value of $\geq$ 481 ms is obtained at any time after C1D1, study treatment must be interrupted, repeat ECG 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. Local cardiologist ECG assessment may be performed at any time during the study at the discretion of the investigator.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. 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 abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.3 Patient reported outcomes

The FACT-B will be used to explore patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms and treatment-related side effects in selected countries including United States, Canada, United Kingdom, France, Italy and Spain. The FACT-B (Brady MJ 1997) is a recognized, reliable and valid instrument frequently used in clinical trials of patients with advanced or metastatic breast cancer.

[redacted]

Due to the nature of the questionnaire and validation, only females will be asked to complete this questionnaire.

The FACT-B quality of life questionnaire (see Appendix 14.2) will be administered at study site before any study drug administrations at the visits indicated in Table 7-1 and Table 7-6 utilizing electronic device for data collection. Collection of the FACT-B PRO has up to -3 day window unless otherwise indicated.

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

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

If an AE or SAE is confirmed then the physician should record the event as instructed in Section 8 of this protocol. Investigators should not encourage the patients to change responses reported in questionnaires.

Table 7-6 Patient reported outcomes collection plan

Patient Questionnaires	Cycle	Day	Time
FACT-B	Cycles 1 to 6	Every cycle during the first 6 cycles	At the beginning of the study visit prior to any interaction with the study investigation.
	Cycle 7 and subsequent cycles	Every 2 cycles: Cycle 8,10,12 Every 3 cycles after that: 15, 18, etc.	
	End of treatment	Day of end of treatment assessment	

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant,

[redacted]

require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met.
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown).

If the event worsens the event 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.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

[redacted]

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the 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 criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- 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
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:

[redacted]

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (i.e. to perform study related assessments)
- 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

- Note that treatment 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 is not a serious adverse event

8.2.2 Reporting

To ensure patient safety every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including 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. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the 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 SAE submission process and requirements for signatures 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 re-occurrence, 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 continues, if and how it was treated, whether the blind was broken or not, 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 Novartis study treatment, an oncology 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 drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not Applicable.

8.4 Pregnancies

This trial is planned for men, post-menopausal women or premenopausal women with ovarian suppression, so no pregnancies are expected for study patients. However, in the rare cases when this occurs, to ensure patient safety, each pregnancy occurring while the patient is on study treatment 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 Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator's Brochure] (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not Applicable.

8.7 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review 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 a Steering Committee charter.

[redacted]

9 Data collection and management

9.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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 recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (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 eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

This study will use Electronic Data Capture (EDC) and the 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 be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.3.1 IRT data collection

Patient eligibility and enrollment will be tracked using an Interactive Response Technology. The data will be entered by the designated investigator staff. The system will be supplied by a vendor, who will also manage the database for that system.

9.3.2 FACT-B questionnaire data collection

FACT-B questionnaire data will be entered using ePRO. The data will be entered by the patients at the clinic. The system will be supplied by a vendor, who will also manage the database for that system.

The use of electronic data collection of clinical outcome assessments (eCOA), including PROs, has been endorsed as standard. The use of both eCOA and paper PRO collection of the same COA measure in a single study is not endorsed. However, paper PRO may be utilized as a backup should there be a failure with the electronic version/system.

All questionnaires should be administered in the patient's local language prior to any interaction with the study investigator. This is to avoid potentially biasing patients or their responses to study questionnaires.

9.4 Database management and quality control

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

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

PRO data will be collected electronically and processed centrally and the results will be sent electronically to Novartis.

[redacted]

Data about all study treatments dispensed to the patient will be tracked using an Interactive Response Technology. The IRT system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Novartis and/or a designated CRO will perform all analyses. Any data analysis carried out independently by the investigator should not be presented or published before the final analysis is completed. The data from all centers that participate in this trial will be combined in the analyses.

Final analyses will be performed when all patients have been followed for 30 days after they have either prematurely discontinued ribociclib or been discontinued from the study after completing treatment as per protocol (see Section 4.1). Data collected during the Extension Phase may be summarized in a separate report or publication. However, analysis may be performed to support regulatory submission or safety update if deemed necessary before the final analysis.

Following subgroup analyses may be performed if deemed necessary at interim and/or final analysis:

- Region (Latin American, Region Europe, Asia)
- Country (countries with at least 100 patients such as US, Canada, Italy, Spain, France, Belgium, Czech Republic)
- Menopausal status (pre/post)
- Prior treatments for (neo)adjuvant (no treatments, endocrine only, chemotherapy only, both (chemotherapy and endocrine treatment))
- ECOG PS (PS 0, 1, and 2)
- Location of metastasis disease (bone, liver, lung, lymphonodes, and etc.)
- Number of metastatic sites (0, 1, 2, ≥3)
- Age (<65, 65-70, 70-75, >75 years)
- Gender (male and female)
- Race (Asian vs. Non-Asian)

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

[redacted]

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who receive at least one dose of study medication defined as either ribociclib or letrozole or goserelin/leuprolide (if applicable) in the Core Phase.

10.1.2 Safety set in Core Phase

The Safety Set includes all patients who received at least one dose of study medications defined as either ribociclib or letrozole or goserelin/leuprolide (if applicable). For this study, the definition of FAS is the same as that of Safety set in Core Phase.

10.1.3 Safety Set in Extension Phase

The Safety set in the Extension Phase includes all patients who received at least one dose of study medications defined as ribociclib or letrozole or goserelin/leuprolide (if applicable) in the Extension Phase.

10.1.4 Per-Protocol set

Not applicable.

10.1.5 Dose-determining analysis set

Not applicable.

10.1.6 Pharmacokinetic analysis set

Not applicable.

10.1.7 Other analysis sets

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

10.2 Patient demographics/other baseline characteristics

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

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

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

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set in Core Phase will be used for all analysis of relevant data (dosing information, use of concomitant therapies, etc.) in the Core Phase, and the safety set in Extension Phase will be used for analysis of all data in the Extension Phase. Categorical data will be summarized as

[redacted]

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

Duration of study treatment exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment. In addition, the duration of exposure to study treatment will be categorized into time intervals; frequency counts and percentages will be presented for the number of patients in each interval.

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

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.

10.4 Primary objective

The primary objective of this study is to further evaluate the safety and tolerability of ribociclib in combination with letrozole in men and postmenopausal women with HR+, HER2- aBC who received no prior hormonal therapy for advanced disease. For details see Section 10.5.3.

10.4.1 Variable

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

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

10.4.2 Statistical hypothesis, model, and method of analysis

No statistical hypotheses will be tested in this study. The primary safety variable (AEs, Grade 3/4 AEs and SAEs, events of special interest, and AEs leading discontinuation and deaths) will be summarized by count and percentage in safety set.

10.4.3 Handling of missing values/censoring/discontinuations

All attempts will be made to ensure that the database contains full information for all safety data. No imputation will be applied for missing data.

10.4.4 Supportive and Sensitivity analyses

Not applicable.

[redacted]

10.5 Secondary objectives

10.5.1 Secondary objective(s)

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

The following endpoints as defined by RECIST1.1 will be use key secondary objectives:

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

Time to progression (TTP) is defined as time from date of start of treatment to the date of event defined as the first documented progression or death due to underlying cancer (Appendix 14.3: Novartis RECIST Guideline v 3.2). Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication. When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

Overall response rate (ORR) is defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1.

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 lesion response of stable disease (SD), lasting as per local review, for a duration of at least 24 weeks. CR, PR and SD are defined according to RECIST 1.1 (see Appendix 14.3 for details)

The distribution of TTP will be estimated using the Kaplan-Meier method. The median TTP along with 95% confidence intervals will be presented. Proportions of patients with ORR and CBR as assessed by investigator will be calculated and presented along with the approximate 95% confidence intervals using Clopper and Pearson (1934) exact method.

In addition, PRO will be assessed using FACT-B instrument (See Section 10.5.4).

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

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

10.5.2 Other secondary efficacy objectives

Not applicable.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For safety analyses in the Core Phase, the Safety Set in Core Phase will be used. For safety analyses in the Extension Phase, the Safety Set in Extension Phase will be used. All listings and tables will be presented.

[redacted]

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

1. **pre-treatment period**:

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

Extension Phase: Not applicable.

2. **on-treatment period**:

Core Phase: For patients who discontinue after the Core Phase treatment, on-treatment period is defined as the time from the date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date). For patients who transition to the Extension Phase, on-treatment period is defined as the time from the date of first administration of study treatment to date of last actual administration of any study treatment in the Core Phase.

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

3. **post-treatment period**:

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

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

The safety summary tables will include assessments from the on-treatment period, unless otherwise specified. Further details will be included in the Statistical Analysis Plan (SAP).

All safety data collected in the study will be listed regardless of the study period with data collected during the pre-treatment and post-treatment period flagged.

10.5.3.2 Adverse events (AEs)

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

The 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.

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.

[redacted]

10.5.3.3 Laboratory abnormalities

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. Grade 5 will not be used.

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

- Number and percentage of patients with worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst post-baseline value (on-treatment).

The following listings will be produced for the laboratory data:

- Listing of patients with laboratory values outside the laboratory reference ranges with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades if applicable and the classifications relative to the laboratory normal ranges

10.5.3.4 Other safety data

Vital signs

Other safety data (including ECGs, vital signs and weight) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate. Further details will be included in the Statistical Analysis Plan (SAP).

10.5.3.5 Supportive analyses for secondary objectives

Not Applicable.

10.5.3.6 Tolerability

Tolerability will be studied in terms of dose reductions or drug interruption due to an AE.

10.5.4 Patient-reported outcomes

FACT-B questionnaire will be used to collect patient reported outcome data in this trial. Scores will be added to create subscale and overall scores. A Trial Outcome Index is generated via the addition of the physical well-being, functional well-being, and breast cancer subscales.

No formal statistical tests will be performed for patient-reported outcomes (PRO) data and hence no multiplicity adjustment will be applied. The PRO analysis set will be used for analyzing PRO data.

[redacted]

Descriptive statistics will be used to summarize the subscale and overall scores at each scheduled assessment time point. Additionally, change from baseline at the time of each assessment will be summarized. PRO data may be summarized by country/region.

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

10.6 Exploratory objectives

Not applicable.

10.7 Interim analysis

Interim analyses (IA) may be performed periodically. The first IA is planned to be performed about 12 months after FPFV, and periodically thereafter, if needed, to fulfill regulatory requests, safety updates, or for publication purposes. Subgroup analyses may be performed at interim if deem necessary (based on the number of patients enrolled in each subgroup). Details of the IA will be provided in the SAP.

10.8 Sample size calculation

A sample size of 3,000 patients is planned to be enrolled in this study to detect rare AEs (frequency ~0.1%) with high probability. This will allow for a greater precision when reporting rare, but clinically meaningful AEs (e.g. febrile neutropenia, QT prolongation, renal insufficiency, thromboembolic events, etc.). For example, if the rate of an AE is 0.1%, then the probability of observing at least 1 AEs out of 3000 patients is 95.0%. A sample size of 3,000 patients will allow for a meaningful safety analysis of specific patient subgroup of particular interest. For example, the expected size of male patients may be 30 (~ 0.1% of total population), patients with ECOG PS=2 may be 150 (~5% of total population), and patients with one prior line of chemotherapy may be 300 (~10% of total population). Table 10-1 below provides a 95% confidence interval (CI) and the corresponding width of the 95% CI, with different rates of rare AEs observed in [LEE011A2301] study) for overall population as well as for subgroups of various sizes.

Table 10-1 Confidence Intervals associated with AEs of interest for subgroups

Number of Patients	Number of AE	Rate	Lower 95% CI	Upper 95% CI	Width*
QT prolongation (observed rate = 3.5%)					
30	1	0.0333	0.0008	0.1722	0.1713
150	5	0.0333	0.0109	0.0761	0.0652
300	10	0.0333	0.0161	0.0604	0.0443
3000	99	0.0330	0.0269	0.0400	0.0131
Febrile neutropenia (observed rate = 1.5%)					
30	0	0	0	0.1157	0.1157
150	3	0.020	0.0041	0.0573	0.0532
300	5	0.0167	0.0054	0.0385	0.0330
3000	45	0.0150	0.0110	0.0200	0.0091

[redacted]

Renal insufficiency / creatinine increase (observed rate = 0.5%)					
30	0	0	0	0.1157	0.1157
150	1	0.0067	0.0002	0.0366	0.0364
300	2	0.0067	0.0008	0.0239	0.0231
3000	15	0.0050	0.0028	0.0082	0.0054

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. 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 Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or if applicable, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures. The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator

must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication 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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Male participants will be requested to provide an information form to female partners.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted in a on the publicly accessible database, e.g. such as www.clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of upon study completion (i.e., LPLV), and finalization of the study report the results of this study will be either submitted for publication and/or posted in those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (//.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to //.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies

[redacted]

to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

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12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

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/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. 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 (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 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 onNovartis PK Science Memorandum, Drug-Drug Interaction and Co-Medication Considerations for Novartis Clinical Trials (release date: Jan 2018), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (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) (fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website crediblemeds.org). Please contact the medical monitor with any questions.

Table 14-1 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, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole, indinavir, idelalisib, Ombitasvir,/ Paritaprevir, Ritonavir/ Dasabuvir (VIEKIRA PAK)
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
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

[redacted]

Category	Drug Name
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 herbal include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications or dietary supplements 7 days prior to first dose of study drug.
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, hormonal therapy, including but not limited to all SERMS [including raloxifene], biologic or radiation therapy [except for palliative radiotherapy as outlined in the protocol], and surgery) other than the study treatments must not be given while the patient is on the study medication. If such agents are required, then the patient must discontinue the study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes), or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.
[2] Herbal product
[3] P-gp inducer
[4] The list provided is as of December 2019.Check 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 14-2 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, modafinil, nafcillin, telotristat, lopinavir[5]
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
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT1/2 substrates[4]	Amantadine, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxaliplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium,, and zidovudine
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax.

[redacted]

Category	Drug Name
[1] Sensitive substrates: 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 atazanvir is prohibited when combined with ritonavir (see Table 14-1) [6] Based data that, exposure of cannabidiol (CBD), tetrahydrocannabinol (THC), 11-hydroxy THC, increased by ~2-3 folds when co-administered with ketoconazole (CYP3A4 inhibitor); Stott et al, Springerplus. 2013; 2: 236 Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University “Clinically Relevant” Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.	

14.2 Appendix 2 – Patient Reported Outcomes FACT-B

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

[redacted]

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

[redacted]

FACT-B (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4

[redacted]

14.3 Appendix 3 - 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: 11-Feb-2016 Version 3.1: 29-Nov-2011 Version 3:0: 19-Oct-2009 Version 2:0: 18-Jan-2007 Version 1:0: 13-Dec-2002
Release date:	11-Feb-2016
Authors (Version 3.2):	[redacted]
Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

[redacted]

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]

14.3.1 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 14.3.2 and the definition of best response in Section 14.3.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.3.18 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 14.3.29 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.

14.3.2 Efficacy assessments

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

14.3.3 Definitions

14.3.4 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 14.3.26

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

[redacted]

- **Cystic lesions:**
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.3.5 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 14.3.26.

14.3.6 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.

[redacted]

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET:** can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
    - If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
    - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Physical exams:** Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

[redacted]

- **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 as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and 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.

14.3.7 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 14.3.4.
- **Nodal target**: See Section 14.3.4.

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.

[redacted]

- **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.

14.3.8 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 14-3) and non-target lesions (Table 14-4) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-5) as well as the presence or absence of new lesions.

14.3.9 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.

14.3.10 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.

[redacted]

14.3.11 Nodal lesions

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

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

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

14.3.12 Determination of target lesion response

Table 14-3 Response criteria for target lesions

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

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 14.3.6).

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

[redacted]

- 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 14-3 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements:** In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size:** When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split:** In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced:** Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.

[redacted]

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

14.3.13 Determination of non-target lesion response

Table 14-4 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2].

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

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

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.

[redacted]

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- **Unequivocal progression:** To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.3.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.3.14 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 14.3.15).
- 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 14.3.6.

14.3.15 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 14-5.

[redacted]

Table 14-5 Overall lesion response at each assessment

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

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 14.3.8.

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.

14.3.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.3.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.3.17 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.

[redacted]

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

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

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

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

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

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

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered

PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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

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

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

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

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

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

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

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

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

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

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

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

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at

[redacted]

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).

14.3.18 Time to event variables

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

14.3.19 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.

14.3.20 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.

14.3.21 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.

[redacted]

14.3.22 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 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 w.r.t. censoring foreseen.

14.3.23 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.

14.3.24 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)

[redacted]

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).

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.

14.3.25 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 14.3.23. 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.

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

Assessment date

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

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

Start dates

For all "time to event" variables, other than 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.

[redacted]

- 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 14.3.26).

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.

14.3.27 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 14-6.

Table 14-6 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 14.3.8.

[redacted]

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.

14.3.28 Sensitivity analyses

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

Based on definitions outlined in Section 14.3.25, 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 14-7 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored

[redacted]

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. =Definitions can be found in Section 14.3.25.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.3.25.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

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

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

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

[redacted]

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 14-7 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.3.29 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]

14.3.30 Study/project specific decisions

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

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.3.31 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 7 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
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

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

14.3.32 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

[redacted]

- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

14.3.33 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.3.34 Programming rules

The following should be used for programming of efficacy results:

[redacted]

14.3.35 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.

14.3.36 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.3.25). 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.

14.3.37 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.

14.3.38 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)'.

14.3.39 Study/project specific programming

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

14.3.40 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

[redacted]

- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-7)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 14.3.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

14.3.41 References (available upon request)

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Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

[redacted]

14.4 Appendix 4 - Bone Marrow Reserve in Adults

Table 14-8 Bone Marrow Reserve in Adults

MARROW DISTRIBUTION OF THE ADULT						
SITE		**MARROW wt. (g)**	**FRACTION RED MARROW AGE 40**	**RED MARROW wt. (g) AGE 40**	**% TOTAL RED MARROW**	
CRANIUM AND MANDIBLE	Head: Cranium Mandible	 165.8 16.4	 0.75 0.75	136.6 124.3 12.3	13.1	13.1
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle : 2 Humerus, head & neck 2 Scapulae 2 Clavicles	 26.5 67.4 21.6	 0.75 0.75 0.75	86.7 20.0 50.5 16.2	8.3	**8.3**
STERNUM AND RIBS	Sternum Ribs: 1 pair 2 3 4 5 6 7 8 9 10 11 12	39.0 10.2 12.6 16.0 18.6 23.8 23.6 25.0 24.0 21.2 16.0 11.2 4.6	0.6 All 0.4	23.4 82.6 4.1 5.0 6.4 7.4 9.5 9.4 10.0 9.6 8.5 6.4 4.5 1.8	2.3 7.9	**10.2**
PELVIC BONES	Sacrum 2 os coxae	194.0 310.6	0.75 0.75	145.6 233.0	13.9 22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		3.8

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961

[redacted]