NOVARTIS

Clinical Development

LEE011 (Ribociclib)

Clinical Trial Protocol CLEE011XDE01 / NCT03096847

A national phase IIIb, multi-center, open label study for women and men with hormone-receptor positive, HER2-negative locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole

RIBECCA

Ribociclib for the tr**E**atment of advan**C**ed breast **Ca**ncer

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Approved by the following

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Compound name / number: Ribcociclib / LEE011

Protocol number: CLEE011XDE01

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki.

type/print name

(Investigator)	Signature	Date

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List of abbreviations

aBC	Advanced Breast Cancer
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
β-hCG	β-subunit of hCG gonadotropin – free hCG gonadotropin
BLRM	Bayesian Logistic Regression Model
CBR	Clinical benefit rate
CISH	Chromogen-in situ-Hybridisierung
CNS	Central nervous system
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
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CT	Computed tomography
DDI	Drug-Drug-Interaction
DFS	Disease-free survival
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
ER	Estrogen receptor
FISH	Fluoreszenz-in-situ-Hybridization
FSH	follikelstimulierendes Hormon
GBM	Glioblastoma multiforme
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LPFT	Last Patient First Treatment
LPFV	Last Patient First Visit
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
[redacted]	[redacted]
MTD	Maximum Tolerated Dose
NCI-CTCAE	National cancer institute – common terminolgy criteria for adverse events
NCRNPD	neither complete response nor progressive disease
PD	Progressive disease
PFS	Progression Free Survival
p.o.	*per os*/by mouth/orally
PHI	Protected Health Information

PgR	Progesterone receptor
PR	Partial Response
QTcF	QT corrected for HR using Fridericia's method
ORR	Overall response rate
OS	Overall survival
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable disease
SISH	silver-in situ-Hybridisation
SmPC	Summaries of Product Characteristics
SOD	Sum of Diameter
SOP	Standard Operating Procedure
TTF	Time to treatment failure
TTP	Time to Progression
UNK	Unknown

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
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
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; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol summary

Protocol number	CLEE011XDE01
Title	A national phase IIIb, multi-center, open label study for women and men with hormone-receptor positive, HER2-negative locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole: RIBECCA (Ribociclib for the trEatment of advanCed breast CAncer)
Brief title	Study of ribociclib in combination with letrozole for the treatment of advanced breast cancer
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug;
Study type	Interventional
Purpose and rationale	To support the encouraging results of MonaLEEsa-2, the main purpose of this study is to collect additional efficacy and safety data for the combination of ribociclib and letrozole in a patient population additional to the MonaLEEsa-2 study and to provide access to ribociclib to patients for which available treatment options are not satisfactory treatment alternatives until the drug is approved for this indication. Furthermore, this trial aims at collecting data for the combination of ribociclib and letrozole in the context of current local routine therapy algorithms for the treatment of metastatic and advanced breast cancer. Preclinical and early clinical data suggests that CDK4/6 inhibition play a key role in the treatment of subsets of breast cancer by abrogating endocrine-resistant cell proliferation. Therefore, the addition of a CDK4/6 inhibitor such as ribociclib to standard endocrine therapy (letrozole or letrozole and goserelin for premenopausal patients, respectively) is a promising therapeutic approach that will be explored in this study. Letrozole is the AI that will serve as endocrine combination partner in this study. It has been extensively studied in the postmenopausal setting and was chosen as endocrine combination partner in the pivotal phase III trial MonaLEEsa-2. The present multi-center, open-label, single-arm study aims to evaluate the efficacy and safety, and quality of life for the combination of ribociclib and letrozole in a patient population in addition to the MonaLEEsa-2 study, i.e. in patients pretreated with one line of chemotherapy and/or a maximum of two lines of endocrine therapy, in premenopausal patients, without

	limitations regarding the progression free interval after adjuvant therapy as well as in men with hormone receptor positive, HER2-negative breast cancer. The exploratory objectives of this study will collect data, are hypothesis generating and will cover analyses of crucial scientific interest, [redacted]
Primary Objective	• The primary objective of this study is the assessment of the clinical benefit rate for the total population and for cohorts A and B separately: o To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole among postmenopausal women and men who received no prior treatment for advanced disease. (approx.70% of patients, cohort A). o To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole and goserelin among pre-, and perimenopausal women who received no prior treatment for advanced disease as well as pre-, peri- and postmenopausal women and men who received prior treatment for advanced disease (approx. 30% of patients, cohort B).
Secondary Objectives	• To assess the clinical benefit rate (CBR) after 24 weeks among pre-, peri- and postmenopausal women and men without prior therapy for advanced disease. • To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib among pre-, peri- and postmenopausal women and men who were pretreated for advanced disease. • To assess progression-free survival (PFS) for the three different populations (postmenopausal women or men without prior treatment for advanced disease, pre- or perimenopausal women without prior treatment for advanced disease, pre-, peri-, or postmenopausal women or men pretreated for advanced disease). • Overall survival (OS) for the three different populations, defined as the time from date of start of treatment to date of death due to any cause. • Overall response rate (ORR) for the three different populations, defined as complete response or partial response as defined by RECIST 1.1

	• To evaluate the safety and tolerability of ribociclib in combination with letrozole (and goserelin in premenopausal patients). • To evaluate patient reported outcomes for health-related quality of life.
Study design	This is a national, multi-center, open-label, phase IIIb trial to determine the efficacy and safety of treatment with ribociclib (LEE011) plus letrozole in women and men with HR+, HER2-negative advanced or metastatic breast cancer.
Population	This study will be performed in 500 patients with hormone receptor positive locally advanced or metastatic breast cancer progressing as defined by: • Cohort A: approx. 70% of patients must be postmenopausal women or men without any treatment for advanced disease • Cohort B: approx. 30% of patients can be pre- or perimenopausal or postmenopausal women or men, must have no more than 1 chemotherapy line for advanced disease, and a maximum of 2 lines of endocrine therapy for advanced disease (or a combination of these criteria). Patients must have documented evidence of recurrence or progression during or after the last therapy prior to enrollment.
Inclusion criteria	• Patient is an adult, ≥ 18 years old at the time of informed consent and has signed informed consent before any trial related activities and according to local guidelines. • Patients with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy. • Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive and HER2-negative breast cancer by local laboratory. Local pathology is sufficient for assessment. • Patient must have either: o Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (Tumor lesions previously irradiated or subjected to other locoregional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented). o Bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease o Non-measurable disease • Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. • Patient has adequate bone marrow and organ function.

Exclusion criteria	• Patient who received any CDK4/6 inhibitor or any mTOR inhibitor. • Patient has a known hypersensitivity to any of the excipients of ribociclib or letrozole. • Patients with current inflammatory breast cancer. • Patient has received > 1 chemotherapy for the treatment of advanced/metastatic breast cancer. Patient has received > 2 endocrine therapies for the treatment of advanced/metastatic breast cancer. Patient has central nervous system (CNS) involvement. If patient is fulfilling the following 3 criteria she/he is eligible for the trial. o completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study and o CNS tumor is clinically stable at the time of screening and o Patient is not receiving steroids and enzyme inducing anti-epileptic medications for brain metastases • Patient has active cardiac disease or a history of cardiac dysfunction.
Investigational and reference therapy	Ribociclib 600mg in combination with letrozole 2.5mg. Premenopausal patients will additionally receive goserelin; men may also be treated with goserelin at the discretion of the investigator.
Efficacy assessments	• CT every 12 weeks until disease progression, death, withdrawal of consent, loss to follow-up, or subject decision. • Brain CT or MRI as clinically indicated. • Whole body bone scan (unless performed within 56 days prior to C1D1). • Bone X-ray, CT (if bone lesion at screening) every 12 weeks • Survival status regardless of treatment.
Safety assessments	• Physical examinations • ECOG performance status • Height, weight, and vital signs • 12 lead ECGs • Laboratory assessments including hematology, biochemistry, lipid panel, hepatic safety markers, and urinalysis • NCI-CTCAE assessment
Other assessments	[redacted]

	[redacted] **Patient-reported outcomes:** Patient questionnaires (EORTC-QLQ-C30, BR-23) will be collected to assess health-related quality-of-life, health status, functioning, disease symptoms, side effects, and cancer-related pain.
Data analysis	The primary objective of this study is the assessment of the clinical benefit rate following RECIST 1.1 for the total population and for cohorts A and B separately: • To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole among postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no prior treatment for advanced disease (Cohort A). • To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole and goserelin among pre-, and perimenopausal women who received no prior treatment for advanced disease as well as pre-, peri- and postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no more than 1 prior chemotherapy and 2 prior lines of endocrine therapy for advanced disease (Cohort B) In this single-arm trial, the primary objective is to estimate the CBR. Therefore, no statistical hypothesis or model is underlying the analysis. The CBR (best overall response of CR or PR or SD) as well as individual response categories (CR, PR, SD, PD, NCRNPD or unknown) will be summarized using frequency tables together with their associated two-sided exact 95% confidence intervals (Clopper-Pearson method). The Full Analysis Set will be used for the primary efficacy analysis.
Key words	HR-positive, HER2-negative, advanced breast cancer, ribociclib, letrozole, CDK4/6, Phase IIIb, ER-positive, PR-positive, postmenopausal, premenopausal, metastatic breast cancer

Amendment 4

Study CLEE011XDE01 was initiated on 24-Oct-2016 and enrollment is completed.

Amendment rationale
The current amendment is intended to:

1. Update the dose adjustment and management recommendations for QTcF prolongation. Analyses of preclinical and recent clinical data with ribociclib have demonstrated that ribociclib prolongs the QT interval in a concentration-dependent manner. As a result, this amendment includes an update to the dosage management guidance for patients who experience QTc prolongation.
2. Update the prohibited concomitant medications based on recent compilation of drug-drug interaction and co-medication considerations
3. Correct minor mistakes in the protocol.

Changes to the protocol
Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Section 4.3 and 7.1.3.1: clarification of end of study
- Section 6.1.1.1: updated guidance related to herbal or dietary supplements.
- Section 6.2.1.2: Additional follow-up for hepatic toxicities updated to include information on the LEE011X2109 study as well as updated text to mandate discontinuation, when liver test elevation is not due to cholestasis.
- Section 6.2.1.4.1: Adjustment of starting dose in special populations updated to include information on the LEE011A2116 study
- Table 6-5: dose adjustment and management recommendations for QTcF prolongation updated
- Section 6.2.2 Anticipated risks and safety concerns of the study drug corrected
- Section 6.3.2: Concomitant therapy requiring caution- updated information on concomitant therapy requiring caution
- Section 6.3.3: Prohibited concomitant therapy- updated list of prohibited concomitant therapy
- Section 6.4.4: Drugs with QT prolongation- further clarified the co-administration of drugs with known risk of torsades de pointes (TdP)
- Section 7.1.1: Rescreening clarified
- Section 7.2.2.3: Mistake corrected: Cycle 1 Day 15 deleted
- Table 7-1 and 7-4: ECG Collection Plan updated
- Section 8.1.1: Mistake corrected: death form deleted
- Section 14 Appendix 1: Concomitant medications: list of prohibited concomitant medications updated based on the oncology clinical pharmacology guidance, drug-drug interaction and co-medication considerations (v07, release date: Jan2018)
    - Table 14-1 : List of prohibited medications during study drug treatment
    - Table 14-2: List of medications to be used with caution during study drug treatment

Amendment 3

Study CLEE011XDE01 was initiated on 24-Oct-2016 and enrollment is currently ongoing.

Amendment rationale
The current amendment is intended to correct mistakes in the protocol.

Changes to the protocol
Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.
The changes being made to the protocol due to this amendment are incorporated in the following sections:

- General: change of name from [redacted] to [redacted], due to marriage
- Section 5.2: inclusion criterion #3: tubal ligation deleted because this is no criterion for postmenopausal status
- Section 5.2: inclusion criterion #12: typo corrected
- Section 6.3.1: concomitant therapy until Safety Follow Up added to match with Table 7-1
- Section 6.6: replacement of the word "ribociclib" with the word "study drug", for clarification purpose
- Section 7.1: FSH/estradiol measurement clarified
- Table 7-1: Mistake corrected: Assessment of Vital signs, Weight, Physical examination, ECOG status, Height changed from C12D1 to C13D1
- Section 7.2.4: editing the following sentences for purpose of clarification:
  "Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, must be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs. This review should be documented in the study sources.
  If an AE or SEA is confirmed then the investigator should record the event as instructed in Section 8 of this protocol. Investigator should not encourage the patients to change responses reported in questionnaires.
  Upon radiologic progression according to RECIST 1.1 treatment with study drug may be continued at the discretion of the investigator until a clinically symptomatic progress occurs. In this case, the quality of life questionnaires must be completed according to Visit schedule. If radiologic progression occurs, before Cycle 13 monthly and after Cycle 13 every 12 weeks until symptomatic progression or End of study as well as upon symptomatic progression."

Amendment 2

Study CLEE011XDE01 was initiated on 24-Oct-2016 and enrollment is currently ongoing.

Amendment rationale

The current amendment is intended to update the existing information about ribociclib, to clarify specific aspects of the original protocol and [redacted] 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.
- Male patients entering the study may also receive 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.
- Upon radiologic progression, according to RECIST 1.1, patients may continue to receive study medication until a clinically symptomatic progression occurs. This decision is at the discretion of the investigator.

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 underline for insertions.
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: Typographical and grammatical corrections.
- Section 1: Updated based on new data from ongoing and completed trials with ribociclib.
- Section 1.2.6: Added CLEE011A2301 (MONALEESA-2) trial key efficacy and safety results of pre-planned interim analysis. Also updated results of CLEE011X2107 trial.
- Section 2.4: Updated trial results.
- Section 5.2: inclusion criteria numbers added.
- Section 5.2: inclusion criterion #3: clarification of postmenopausal status added.
- Section 5.2: inclusion criterion #4: added explanation for Cohorts A/B.
- Section 5.2: inclusion criterion #9: rephrased for clarification.
- Section 5.2: inclusion criterion #11: creatinine clearance added, Morbus Meulengracht added.
- Section 5.2: inclusion criterion #12: clarification for corrected calcium added.
- Section 5.3: exclusion criterion #6 and #7: pretreatment with aromatase inhibitor therapy for up to 21 days not counted as therapy line; wash-out period for previous treatment deleted and note regarding overlapping toxicity added.
- Section 5.3: exclusion criterion #10: deleted as this is a requirement with Fulvestrant as combination partner, not letrozole.

- Section 5.3: exclusion criterion #12: deleted because concomitant palliative radiotherapy is allowed.
- Section 5.3: exclusion criterion #17: Dietary supplements are allowed if they contain only nutrients, minerals and/or vitamins.
- Section 5.3: exclusion criterion #21: hormonal contraception methods deleted.
- Section 6.1: added goserelin as treatment option for men; permitted dietary supplements added.
- Section 6.1.2: [redacted]
- Section 6.2.1.1: information regarding inadvertent dosing of ribociclib on a rest day.
- Section 6.2.1.1, Table 6.3: leukocyte count added, recommendation for Grade 3 Neutropenia updated.
- Section 6.2.1.3, Table 6-5: QTc changed to QTcF, asterisk removed.
- Section 6.2.1.4: information on bisphosphonate use and calcium added.
- Section 6.2.1.4.1: Updated information on renal impairment and hepatic impairment added.
- Section 6.3.1: concomitant therapy 30 days before study start added.
- Section 6.3.1.4: information about irradiated lesions added.
- Section 6.3.3: dietary supplements allowed.
- Section 6.4.2: treatment assignment clarified.
- Section 6.5: clarification of study drug dispensing updated.
- Section 6.5.2: temperature log information updated.
- Section 7.1: Visit evaluation schedule updated according to changes made in Amendment 2.
- Section 7.1.1: Rescreening added as option.
- Section 7.1.1.2: Updated required assessments.
- Section 7.1.2: Men added to goserelin section.
- Section 7.1.5: Survival follow up added.
- Section 7.2.1: Time window for radiologic assessments changed from +/- 3 to +/- 7 days; color photography of skin lesions added.
- Section 7.2.1.1: Section added for treatment beyond progression.
- Section 7.2.2.4: INR added in Table 7-3; information of urinalysis type added (dipstick); simultaneous FSH and/or Estradiol measurement should be performed with pregnancy tests.
- Section 7.2.4: Collection schedule for QoL questionnaires updated.
- Section 8.2.2: added information that an SAE that is considered completely unrelated, to a previously reported one should be reported separately as a new event.

Amendment 1

Study CLEE011XDE01 has not yet been initiated. No patients have been enrolled so far.

Amendment rationale

The purpose of this amendment is to include feedback received from BfArM and ECs during the assessment of the initial application.

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Role of the 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 (SERM; tamoxifen), ER antagonists (fulvestrant), selective 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 13 2013).

1.1.2 Role of cell cycle related genes and proteins in cancer

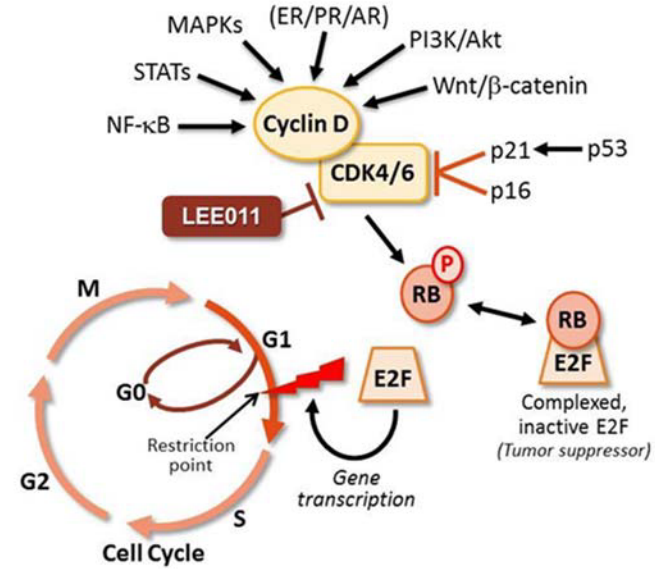
In the mammalian cell cycle, entry into S phase is achieved by cyclin-dependent kinases 4 and 6 (CDK4/6). The cyclin D proteins act through the CDK4 and CDK6 protein kinases (positive regulators) to promote G1 progression (Musgrove 2011). CDK4 and CDK6, in turn, hyperphosphorylate and activate the retinoblastoma protein (pRb) to promote cell cycle entry and cell proliferation (Figure 1-1). Mitogenic signals converge at the level of cyclin D1 upregulation and CDK4/6 association, localization, and kinase activity. CDK4/6 phosphorylates and inactivates Rb tumor suppressor proteins, leading to dissociation of E2F transcription factors and transcriptional regulation of genes important for G1/S transition and cell cycle progression through the restriction point.

D-cyclins are the positive regulators of these kinases, while the p16 protein encoded by the INK4a gene functions as their major inhibitor. Upon mitogen stimulation, signal transduction pathways including MAPK and PI3K increase cell proliferation by upregulating the expression of D-cyclins, which in turn activate the kinases.

A wide range of human tumors harbor genetic aberrations that increase the activity of CDK4/6. Furthermore, focal copy number abnormalities that result in increased CDK activity are among the most commonly described mutations observed in diverse tumor types; these mutations include amplifications of the genes that encode cyclin D1 or CDK4, and deletions affecting the *CDKN2A* locus, which encodes the $p16^{INK4a}$ inhibitor of CDK activity (Beroukhim 2010). Finally, the pRb is a tumor suppressor protein that is dysfunctional in several major cancers (Murphree and Benedict 1984). Direct analyses of primary tumors have revealed loss of pRb expression in 20-35% of tumors, and loss of

heterozygosity or other alterations of the pRb locus in 7.4% of tumors (Pietilainen 1995; Borg 1992; Oesterreich 1999; Chano 2002).

Figure 1-1 Regulation of cell cycle checkpoint control



Adapted from Lange and Yee (2011).

Refer to ribociclib Investigators Brochure for more details.

1.1.3 Role of cyclin D kinases inhibitors in breast cancer

Cell cycle related genes and proteins are frequently deregulated in breast cancer. Approximately 15%-20% of human breast cancers exhibit amplification of the cyclin D1 (CCND1) gene (Buckley 1993; Dickson 1995; Lundgren 2012) while the majority of human mammary carcinomas overexpress CCND1 protein (Bartkova 1994; Gillett 1994; McIntosh 1995; Gillet 1996). Overexpression of CCND1 is seen early in breast cancer, and it is maintained at all stages of breast cancer progression, including metastatic lesions (Bartkova 1994; Gillett 1994; McIntosh 1995) and the continued presence of CDK4-associated kinase activity is actually required to maintain breast tumorigenesis (Yu 2006).

Data from the Cancer Genome Atlas highlight the importance of the Cyclin/CDK/Rb pathway in luminal breast cancer (The Cancer Genome Atlas Network 2012). Abnormalities that result in CDK activation are highly enriched in the luminal A and B molecularly defined subgroups, approximately 85% of which were ER+/HER2$^-$negative. Cyclin D1 amplifications were observed in 29% and 58% of the luminal A and B subtypes, respectively, and CDK4 amplifications were observed in 14% and 25% of luminal A and B subtypes, respectively. Luminal A subtype tumors also have loss of CDKN2C, which encodes p16^{INK4a}, a CDK inhibitor. Although In preclinical models, pRb depletion appears to be associated with resistance to antiestrogen therapy (Bosco 2007), the luminal subtypes also maintain expression of Rb (The Cancer Genome Atlas Network 2012), which would be essential for benefit from treatment with a CDK4/6 inhibitor. Of note, the p16^{INK4a} gene promoter is transcriptionally active in senescent, but not non-senescent cells (Baker 2011). Furthermore, recent data exploring 47 human breast cancer cell lines demonstrated preferential sensitivity to CDK4/6 inhibitors in ER/HER2+ cell lines (Finn 2009). Finally,

recent preclinical data suggest that despite estrogen deprivation, ERα retains genomic activity and drives a CDK4/E2F dependent transcriptional program (Miller 2011).

Ibrance® (palbociclib) is a CDK4/6i, inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with hormone receptor (ER)-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for metastatic disease (Ibrance® Prescription Information). A randomized, open-label, multicenter study of palbociclib plus letrozole versus letrozole alone conducted in 165 postmenopausal women with ER-positive, HER2-negative advanced breast cancer with no previous systemic treatment for their disease showed a statistically significant improvement in PFS with the addition of palbociclib to letrozole (median PFS 20.2 months versus 10.2 months (HR 0.49; 95% CI:0.32 to 0.75; P=0.0004) (Finn 2014). This was confirmed in a randomized, multicenter, double-blind phase 3 study of palbociclib plus letrozole versus placebo plus letrozole in postmenopausal women who had not received any prior systemic anti-cancer treatment for advanced disease. The median PFS in this study was 24.8 months for the CDK4/6 inhibitor in combination with letrozole versus 14.5 months for placebo plus letrozole (HR=0.58 [0.46 to –0.72], P<0.000001). (Finn et al., Abstract 507, oral presentation at ASCO 2016, Chicago)
A phase III study in 521 patients with advanced HR+, HER2-negative advanced BC that had relapsed or progressed during prior endocrine therapy showed a median PFS of 9.2 months (95% CI, 7.5 to not estimable) with palbociclib in combination with fulvestrant vs 3.8 months (95% CI, 3.5 to 5.5) with placebo and fulvestrant (HR for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001) (Turner 2015). In this study, premenopausal and postmenopausal patients were enrolled and consistent benefit from palbociclib was seen in pre- and post-menopausal women. Pre- and peri-menopausal women also received goserelin in addition to the study medication. The relative difference in progression-free survival between palbociclib and placebo was similar in premenopausal or perimenopausal patients and postmenopausal patients (hazard ratio for disease progression or death, 0.44 and 0.41, respectively; P = 0.94 for interaction between the study-drug assignment and menopausal status) (Turner 2015).

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

1.2.1 Overview of ribociclib

Ribociclib (LEE011) is an orally bioavailable and highly selective small molecule inhibitor of the CDK4/cyclin-D1 and CDK6/ cyclin-D3 enzyme complexes with IC50's of 0.01 and 0.039 µM in biochemical assays, respectively. Refer to ribociclib Investigators Brochure for details.

1.2.1.1 Nonclinical experience of ribociclib

1.2.1.1.1 Nonclinical pharmacology of ribociclib

A panel of human breast cancer cell lines was treated with increasing doses of ribociclib and dose-dependent inhibition of proliferation was observed across the panel with enhanced activity against ER+ breast cancer cell lines with IC50 < 1µM being observed for most ER+ breast cancer lines (Novartis internal data, ribociclib Investigator Brochure figure 4-3). Ribociclib as a single agent has been shown to have activity in preclinical models of ER+ breast cancer (Novartis internal data). In in- vivo- studies, combinations

with the mTOR inhibitor RAD001 and PI3K inhibitor, BYL719, resulted in either improved or prolonged anti-tumor effects in tumor models derived from ER+ breast cancer.

In Jeko-1 MCL cells that overexpress cyclin D1 as a result of the t(11;14) chromosomal translocation, LEE011 inhibits the phosphorylation of pRb at CDK4/6-specific sites with an average IC_{50} of 60 nM. In nude rats bearing Jeko-1 subcutaneous xenografts, ribociclib demonstrates dose-dependent target inhibition in the tumors. LEE011 doses that induce >75% inhibition of pRb phosphorylation in this model are associated with complete tumor regression (see ribociclib Investigator Brochure Sections 4.1.1.2.1, 4.1.1.2.2). Ribociclib also inhibits the growth of many other tumor cell types in vitro and in vivo, including liposarcoma, melanoma, rhabdoid cancer, and carcinomas of the esophagus, breast, lung and pancreas. 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. Refer to ribociclib Investigators Brochure for more details.

Preclinical data generated using a primary model of ER+ breast cancer compared ribociclib at clinically relevant doses with the combination of ribociclib plus letrozole (ribociclib Investigator Brochure Figure 4-10). Animals treated with the combination showed complete inhibition of tumor growth. Body weight was monitored throughout the treatment showing comparable results in all groups supporting the predicted lack of overlapping toxicity between ribociclib and letrozole.

1.2.1.1.2 Nonclinical pharmacokinetics and metabolism of ribociclib

The pharmacokinetics (PK) of ribociclib was investigated in mouse, rat, dog and monkey. Ribociclib showed high clearance (CL) in the mouse, rat, dog and monkey. The volume of distribution was large across species and the terminal elimination half-life ($T_{1/2}$) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h).

Bioavailability was low to moderate in rat (37%) and cynomolgus monkey (17%); moderate in mouse (65%) and dog (64%). Following oral administration, time to reach maximal plasma concentrations (T_{max}) occurred between 2 to 4 h across species.

Gender dependent toxicokinetics were observed in rats with higher exposure to ribociclib in males as compared to females and higher exposure to the metabolite, LEQ803. Plasma protein binding was moderate in all species (unbound fraction (fu) in human: 30%).

In a rat ADME (absorption, distribution, metabolism and excretion) study, extensive distribution of [3H]-ribociclib and its metabolites was observed. In pigmented rats, radioactivity was specifically found in melanin-containing structures; the highest exposure to total radiolabeled components was observed in eye ciliary body, eye choroid, meninges, tactile hair and hair follicles. Radioactivity was not detected in the brain. T_{last} (last observation timepoint) was ≤ 48h for most tissues, but long (168 to 840h) for lymph nodes, preputial gland, testis, eye and meninges. At one week ≤ 0.04% of the dose was retained in the carcass. LEQ803 (N-demethylation) was a prominent metabolite found in mouse, rat, dog, monkey and human hepatocytes. This metabolite retains some pharmacologic activity and interacts with human Ether-a-go-go Related Gene (hERG) channels in vitro. In male rats, unchanged ribociclib (24.7% of [3H]AUC_{0-24h}) and its metabolite M11 (26.3% of [3H]AUC_{0-24h}) were the major components in plasma.

In rats, ribociclib was eliminated mainly by metabolism with direct sulfation as the major pathway. Direct ribociclib secretion accounted for 18.2% of the total plasma clearance. In male dogs, metabolism was the major elimination route. The most prominent components in

plasma were ribociclib (55.9% of [14C]AUC_{0-48h}) and its metabolite LEQ803 (1.61% of [14C]AUC_{0-48h}).

Results from the ADME (male rats) study showed that 3H-components were predominantly excreted with bile (61.4% of dose). Minor urinary excretion was observed (5.9% of dose after p.o.). The majority of the administered dose (87.3%) was excreted within 24 h via urine, feces (enteric secretion) and bile.

In vitro, ribociclib was a reversible inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. Ribociclib may inhibit CYP3A4 under therapeutic conditions. No induction of CYP1A2, CYP2B6 or CYP3A4 was observed. The in vitro inhibitory potency of ribociclib observed for the transporters OATP1B1 (organic anion transporting polypeptide 1B1), BCRP (breast cancer resistance protein), OCT1 (organic cation transporter 1), OCT2, MATE1 (multidrug and toxin extrusion protein 1), MATE2K and BSEP (bile salt export pump) 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). The elimination of ribociclib may be affected by co-administered drugs that inhibit or induce CYP3A4. 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 ribociclib Investigators Brochure for more details.

1.2.1.2 Clinical experience with ribociclib

Ribociclib is currently being investigated in patients as a single agent in 3 phase I studies: (CLEE011X1101, CLEE011X2101, CLEE011X2102) in 2 phase II studies: (CLEE011X2201, CLEE011XUS03).
Ribociclib is being evaluated in several combination trials: letrozole (CLEE011A2201, CLEE011A2301, CLEE011A2115C), letrozole and alpelisib (CLEE011X2107), letrozole and buparlisib (CLEE011A2112C); goserelin, letrozole, anastrozole, and tamoxifen (CLEE011E2301); fulvestrant (CLEE011F2301), fulvestrant and buparlisib (CLEE011X2108), everolimus and exemestane (CLEE011X2106), ceritinib (CLEE011X2110C) LDK378 (CLEE011X2110C), HDM201 (CHDM201X2103C), LGX818 (CLEE011X2105, CLGX818X2102), LGX818, MEK162 (binimetinib) buparlisib or LGX818, binimetinib and INC280 or LGX818, binimetinib and BGJ398 (CLGX818X2109) binimetinib (CMEK162X2114), or binimetinib and LGX818 (CMEK162X2110).
These trials are ongoing with the exception of CLEE011A2201 and CLEE011A2112C where recruitment was prematurely terminated on 28-July-2014 and 20-Mar-2015 respectively. CLEE011A2301, CLEE011X2102 and CLEE011X2105 have also closed enrolment. The results of the phase I combination of letrozole and LEE011 (CLEE011X2107) are detailed in Section 1.2.6. The phase III trial CLEE011A2301, investigating the combination of letrozole and ribociclib, reached its primary endpoint prematurely at the preplanned interim analysis.

Ribociclib is also being investigated in 4 clinical pharmacology studies: CLEE011A2102, CLEE011A2103, CLEE011A2109 and CLEE0112116. Three clinical pharmacology studies in healthy subjects have been completed: CLEE011A2101, CLEE011A2106 and CLEE011A2111.
Refer to the ribociclib Investigator Brochure for additional details.

1.2.1.2.1 Clinical safety of ribociclib as single agent

As of 15-Jun-2015, 157 patients have been treated with single agent ribociclib in the first-in-human (FIH) phase I study; 85 patients have been treated in the initial dose escalation part for the 3 week on/1 week off regimen and 47 patients in the dose expansion part of the study; 18 patients were enrolled for the continuous dosing regimen with ribociclib and, 7 patients were enrolled in the liquid formulation cohort.

Patients with advanced solid tumors or lymphomas were treated with increasing doses of ribociclib orally, once daily (qd) for 21 days followed by a 1-week rest (28-day cycle). Doses ranging from 50 mg to 1200 mg were evaluated on this schedule. Treatment has been discontinued in 120 (90%) patients; the primary reasons for treatment discontinuation were: disease progression (106 [80%] patients); adverse events (AEs) (7 [5%] patients); death (2 [1.5%] patients); withdrawal of consent (3 [2%] patient); and loss to follow up (1 [1%] patient).

The most frequently reported AEs (≥10%), regardless of grade, causality and ribociclib dose were: nausea (52.3%); fatigue (40.9%); diarrhea (37.1%); vomiting (35.6%); neutropenia (34.1%); anemia (32.6%); decreased appetite, thrombocytopenia (23.5% each); white blood cell count decrease (22.7%); leukopenia (22%); constipation (21.2%); dyspnea (20.5%); asthenia (19.7%); cough (18.2%); hyperglycemia (17.4%); headache, hypoalbuminemia (16.7% each); ECG QT prolonged (15.9%); abdominal pain, back pain, lymphocyte count decrease, pyrexia (15.2% each); AST increase, blood creatinine increased, dizziness, lymphopenia (14.4% each); peripheral edema (13.6%); neutrophil count decreased (12.9%); ALT increase, pain in extremity (12.1% each) and hypocalcemia (11.4%).

For either continuous or intermittent dosing, the onset of neutropenia (most frequently Grade 2) occurs by Day 15, reaching a nadir in the third or fourth week with recovery during the week of drug holiday for the three weeks on/one week off schedule. Some patients require additional time for recovery (7 to 14 days). QT changes become evident in the first cycle by Day 8 and later (once steady state is reached), are associated with the maximum drug levels between 1 to 8 h post-dose, and remain stable or improve in subsequent cycles.

As of 15-Jun-2015, asymptomatic Grade 2 QTcF prolongation was observed with increasing frequency when increasing the dose starting at 600 mg: ten patients (13.5%) in the 600 mg cohort, three patients (21%) in the 750 mg cohort, four patients (31%) in the 900 mg cohort, and two patients (67%) in the 1200 mg cohort. Four patients (5.4%) at 600 mg and two patients (15%) at 900 mg had asymptomatic QTcF prolongation that resulted in a QTcF interval of 500 ms or more. As compared to baseline value, QTcF prolongation was at least 30 msec in 2 patients (50%) at 250mg, 2 (40%) at 350 mg and 400 mg, 59 (79.7%) at 600 mg, 11 (78.6%) at 750 mg, 11 (85%) at 900 mg and 2 (67%) at 1200 mg; and at least 60 msec in 23%, 0%, 39% and 67% of patients at 600 mg, 750 mg, 900 mg and 1200 mg, respectively. One grade 1 atrioventricular block of first degree was reported as related to ribociclib given at the dose of 140 mg. One grade 1 atrioventricular block of first degree was reported as related to ribociclib given at the dose of 140 mg. No other cardiac abnormalities were observed as related adverse events in any patient.

There have been no deaths related to study drug reported on study [CLEE011X2101]. The following serious adverse events shown in Table 1-1 have been reported with a suspected causal relationship in study [CLEE011X2101] as of 6-Aug-2015. For a complete list of AEs, all grades and Grade 3/4 that are suspected to be related to ribociclib refer to the ribociclib Investigators Brochure.

Table 1-1 Serious adverse events with a suspected causal relationship with ribociclib single agent

Serious suspected adverse events which have occurred with ribociclib (single agent)	
System Organ Class Preferred Term	**Preferred Term**
Blood and lymphatic system disorders	Anaemia, Febrile neutropenia, Neutropenia, Thrombocytopenia
Gastrointestinal disorders	Diarrhoea, Nausea,*Pancreatitis*
General disorders and administration site conditions	Generalized oedema
Infections and infestations	Herpes simplex
Investigations	***Blood creatinine increased,*** *Electrocardiogram QT prolonged*

Events in *italic font* indicate those events which are newly included since the previous edition of the reference safety information.

Refer to ribociclib Investigators Brochure for more details.

1.2.1.2.2 Clinical efficacy with ribociclib as single agent

Preliminary anti-tumor activity of ribociclib from trial [CLEE011X2101] was assessed across all dose levels (50 mg – 1200 mg). Out of 114 evaluable subjects as of 24-Apr-2014, 3 partial responses were observed at the 600 mg dose level; one each in BRAF/NRAS wild type with CCND1 amplified melanoma, and head and neck acinar carcinoma with CDKN2A loss (both on the 3 weeks on/1 week off regimen), and ER+/HER2-, PIK3CA mutant, CCND1 amplified breast cancer (on the continuous daily dosing regimen). Stable disease (SD) was the best overall response in 41 (37%) patients. Enrollment in this study is completed. Stable disease ≥4 cycles and ≥6 cycles was observed in 26 (24%) and 17 (15%) patients, respectively. Six patients with SD ≥4 cycles received treatment for >1 year, of these 2 patients were on study for >2 years (Jeffrey R Infante ASCO 2014 abstract 2528).

Refer to ribociclib Investigators Brochure for more details.

1.2.1.2.3 Clinical pharmacokinetics of ribociclib

As of 15-Jun-2015, preliminary PK data were available from approximately 143 patients from the first-inhuman (FIH) study [CLEE011X2101] across the dose range of 50 to 1200 mg. Following oral dosing, ribociclib was rapidly absorbed with median T_{max} ranging from 1 to 4 hours. Ribociclib plasma exposure (C_{max} and AUC_{0-24h}) exhibited slightly over-proportional increases in exposure across the dose range tested. Steady-state was generally reached by Day 8 and the mean effective $T_{1/2}$ based on accumulation ratio (i.e., T1/2, acc) ranged from 12.3 to 42.9. The mean accumulation ratio (R_{acc}) calculated from AUC_{0-24h} at steady-state and AUC_{0-24h} after a single dose across the studied doses ranged from 1.35 to 3.11.

At the recommended dose for future development (600 mg), steady-state plasma Cmax (n=56) ranges from 606-6170 ng/mL (geometric mean = 1790 ng/mL or 4.1 µM), median T_{max} (n=72) is 2.1 h, and AUC_{0-24h} (n=53) ranges from 6770-90600 ng*h/mL (geometric mean = 23600 h*ng/mL). At this dose, inter-patient variability in C_{max} and AUC is 62% and 66%, respectively, as assessed by geometric coefficient of variation (CV%). At the 600 mg dose level, LEQ803, an active metabolite of ribociclib, accounted for approximately 8% (geometric mean) of ribociclib AUC_{0-24h} after single and multiple doses. Refer to the ribociclib [Investigators Brochure] for more details.

In a food effect study [CLEE011A2111] in 24 healthy subjects, a single dose of ribociclib (600 mg) was administered as drug-in-capsule (DiC) with a high-fat, high-calorie meal and under fasted conditions. Compared to the fasted state, oral administration of a single 600 mg dose of ribociclib DiC with a high-fat, high-calorie meal decreased the rate of absorption of ribociclib resulting in a 23% decrease in C_{max} (geometric mean ratio: 0.775; 90% confidence interval [CI]: 0.700, 0.858) and a median difference in T_{max} of 2 hours. However, there was no effect on the extent of absorption of ribociclib as the overall exposure (AUC_{inf}) was unaffected under fed conditions (geometric mean ratio: 0.994; 90% CI: 0.925, 1.070). A similar trend was observed for LEQ803, an active metabolite of ribociclib, with a decrease in C_{max} (32%), a delay in median Tmax, and no substantial effect on overall exposure. Based on these data, ribociclib DiC can be taken without regard to meals.

In the human ADME study [CLEE011A2102], a single oral dose of 600 mg [^{14}C]LEE011 was administered to 6 healthy male subjects. The majority of the administered dose was excreted in feces (69.1%), with a minor amount excreted in urine (22.6%). Absorption was estimated to be approximately 58.8%. Ribociclib accounted for approximately 23% of the total radioactivity in plasma, based on AUC_{inf}. Metabolites M1 (glucuronidation of M15), M4 (LEQ803, N-demethylation) and M13 (CCI284, N-hydroxylation) were the most abundant metabolites in plasma, representing an estimated 7.78%, 8.60% and 9.39% of total [$_{14}$C]$AUC_{0\text{-}48h}$, and 17.9%, 19.8% and 21.6% of ribociclib $AUC_{0\text{-}48h}$, based on metabolite profiles.

A DDI study with ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) was conducted in 48 healthy subjects [CLEE011A2101]. Compared to ribociclib alone, ritonavir (100 mg bid for 14 days) increased ribociclib C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single oral dose of 400 mg ribociclib. C_{max} and AUC_{last} decreased by 96% and 98%, respectively. These results demonstrated that concurrent use of strong CYP3A4 inhibitors may markedly increase ribociclib exposure and are prohibited.

Compared to ribociclib alone, rifampicin (600 mg daily for 14 days) decreased ribociclib C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single oral dose of 600 mg ribociclib. C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively. These results demonstrated that concurrent use of strong CYP3A4 inducers may markedly decrease ribociclib exposure and are prohibited.

A DDI cocktail study with midazolam (a sensitive CYP3A4 substrate) and caffeine (a sensitive CYP1A2 substrate) conducted in 25 healthy subjects [CLEE011A2106] indicated that ribociclib (400 mg) is a moderate inhibitor of CYP3A4, but did not have a substantial effect on CYP1A2 substrates in humans. PK data indicated that compared to midazolam and caffeine alone, multiple doses of ribociclib (400 mg qd for 8 days) increased midazolam C_{max} and AUC_{inf} by 2.1-fold and 3.8-fold, respectively. The effect of multiple doses of ribociclib on caffeine was minimal, with C_{max} decreased by approximately 10% and AUC_{inf} increased slightly by 20%. Based on these data, ribociclib (400 mg) is a moderate CYP3A4 inhibitor ($\geq$ 2- fold but < 5-fold increase in AUC). Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index is prohibited.

Ribociclib (400 mg) did not have a substantial effect on CYP1A2 in humans; therefore, concurrent use of CYP1A2 substrates is not expected to lead to clinically significant DDIs.

Refer to the ribociclib Investigators Brochure for more details.

1.2.1.2.4 Clinical pharmacodynamics of ribociclib

Paired skin biopsies from 55 patients treated with LEE011 at doses ranging from 50 to 900 mg and paired tumor biopsies from 20 patients (16 patients at 600 mg, 2 patients at 900 mg, and 1 patient each at 70 and 750 mg) were assessed for changes in Ki67 and pRb levels. Preliminary results indicate the following: in skin biopsies, reductions in Ki67 from baseline were observed across all dose levels with a more consistent trend from 400 mg onwards; in tumor biopsies, reductions in Ki67 from baseline were observed in 18/20 patients; however, limited samples and varied tumor types prevent conclusions about any dose-response relationship from being drawn. Changes in pRb were not significant or consistent in either skin or tumor samples, possibly due to varied tumor types. For further details see Section 5.2.1 of the ribociclib (LEE011) investigator's brochure.

1.2.2 Overview of letrozole

Use of endocrine neoadjuvant therapy was initially restricted to elderly ER+ patients based on the fact that hormone receptor positive tumors were responding less to chemotherapy as compared to other breast cancer types (Gianni 2005; Berry 2006). More recent trials have shown the lack of interaction between neoadjuvant endocrine therapy outcome and age (Olson 2009), and comparable outcome between chemotherapy and endocrine neoadjuvant therapy in ER+ BC patients (Semiglazov 2007). Neoadjuvant endocrine treatment can thus now be proposed to postmenopausal women as neoadjuvant treatment regardless of their age (NCCN guidelines 3.2013).

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 2001).

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].

In the neoadjuvant setting for women with unresectable hormone receptor positive early breast cancer, letrozole was associated with significantly higher response rate than tamoxifen (60% versus 48%, P=0.004) and a higher percentage of patients underwent breast conservative surgery (48% versus 36%, *P*=0.036) (Ellis 2001).

1.2.3 Overview of goserelin

Goserelin (Zoladex®) is a synthetic decapeptide analog of gonadotropin releasing hormone (GnRH) indicated for prostatic carcinoma, endometriosis, endometrial thinning, and advanced breast cancer. Goserelin is administered subcutaneously every 28 days at a dose of 3.6 mg. Following subcutaneous administration of goserelin (3.6 mg for 2 months), T_{max} was 12-15 days post-dose in males and 8-22 days post-dose in females. The metabolism of goserelin is not CYP-mediated; rather it is metabolized by hydrolysis of C-terminal amino acids. More than 90% of a radiolabeled dose was excreted in the urine, with approximately 20% of the dose in urine accounted for by unchanged goserelin. The adverse events occurring in > 20% of women included hot flushes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea and peripheral edema (Zoladex® Prescribing Information).

For information on goserelin and management of goserelin related adverse events refer to the Zoladex® SmPC or Prescribing Information.

1.2.4 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 LEE011 is a reversible inhibitor of CYP3A4 (Ki = 35 µM) and a time-dependent inhibitor of CYP3A4 (KI= 5.06 µM, kinact = 0.0245 min^{-1}). 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 that ribociclib and letrozole exposures are within the range of values for the respective single agent and the combination is safe and tolerable.

1.2.5 Low potential for drug-drug interactions with goserelin

The metabolism of goserelin is not CYP-mediated; rather hydrolysis of C-terminal amino acids is the major clearance mechanism. No formal clinical DDI studies have been conducted or reported with goserelin. Based on the available information, goserelin is not expected to affect the metabolism of nor be affected by co-administered drugs (Zoladex® Prescribing Information).

1.2.6 Summary of available results from patients treated with the combination of ribociclib 600 mg and letrozole 2.5 mg daily

Study CLEE011X2107, is a multicenter phase Ib/II dose escalation/expansion study of LEE011 and BYL719 in combination with letrozole in adult patients with advanced estrogen receptor positive (ER+) breast cancer. Patients must be postmenopausal with metastatic or locally advanced ER+, HER2-negative breast cancer. Dosing in Arm 1 (letrozole 2.5 mg once daily on days 1-28 with LEE011 600 mg once daily on days 1-21 of a 28 day cycle since there is a 7 day rest from LEE011 treatment in each cycle) began on December 3, 2013, and as of October 30, 2015, 47 patients have been treated (dose escalation and dose expansion). 17 of 19 patients (90%) in dose escalation were previously treated for ABC (previously treated group), 27 of 28 patients (96%) in dose expansion were treatment-naïve for ABC (treatment-naïve group).
Treatment has been discontinued in all 19 previously treated pts (100%) due to progression of disease (15 pts [79%]), AEs (2 pts [11%]: Grade 3 alanine aminotransferase increased and Grade 4 myelodysplastic syndrome), and physician decision (2 pts [11%]). Ten pts (36%) in the treatment-naïve group have discontinued treatment due to progression of disease (8 pts [29%]) and physician decision (2 pts [7%]). The median (range) duration of treatment exposure was 16 (9–65) weeks in the previously treated group and 36 (9–74) weeks in the treatment-naïve group; 6 previously treated pts (32%) and 22 treatment-naïve pts (79%) received treatment for ≥6 cycles. Ribociclib dose reductions occurred in 4 previously treated pts (21%; 1 reduction each) and in 4 treatment-naïve pts (14%; 1 reduction each). Ribociclib treatment interruptions due to AEs occurred in 6 previously treated pts (32%) and in 10 treatment-naïve pts (36%).

Table 1-2 Adverse events suspected to be study drug-related (All-Grade ≥15% in all pts)

	Previously Treated Group (n=19)		Treatment-naïve Group (n=28)		All Pts (N=47)	
AE	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Neutropenia	13 (68)	7 (37)	20 (71)	13 (46)	33 (70)	20 (43)
Nausea	7 (37)	0	13 (46)	0	20 (43)	0
Fatigue	7 (37)	0	5 (18)	0	12 (26)	0
Alopecia	0	0	11 (39)	0	11 (23)	0
Anemia	4 (21)	0	7 (25)	0	11 (23)	0
Diarrhea	3 (16)	0	8 (29)	0	11 (23)	0

Asthenia	0	0	10 (36)	0	10 (21)	0
Neutrophil count decreased	3 (16)	2 (11)	5 (18)	3 (11)	8 (17)	5 (11)
ALT increased	1 (5)	1 (5)	6 (21)	1(4)	7 (15)	2 (4)
AST increased	1 (5)	1 (5)	6 (21)	0	7 (15)	1 (2)
Dry skin	0	0	7 (25)	0	7 (15)	0
Headache	2 (11)	0	5 (18)	0	7 (15)	0
Pruritus	0	0	7 (25)	0	7 (15)	0
Vomiting	1 (5)	0	6 (21)	0	7 (15)	0

The median relative dose intensity of ribociclib was >98% in both groups. AEs suspected to be study drug-related (all Grade ≥15% in all pts) are summarized in Table 1-2. The most common (>30% of pts) all-Grade AEs were neutropenia (33 pts [70%]) and nausea (20 pts [43%]). The most common (>5% of pts) Grade 3/4 AEs suspected to be drug-related were: neutropenia (20 pts [43%]), neutrophil count decreased (5 pts [11%]), and white blood cell count decreased (3 pts [6%]).PK data collected from patients in [CLEE011X2107] are summarized in Table 1-3. Ribociclib exposure (C_{max} and $AUC_{0–24h}$; Table 1-3) in combination with letrozole was consistent with ribociclib single-agent data, indicating no PK drug–drug interaction. Ribociclib accumulated 2.4-fold following multiple doses, possibly due to a combined effect of drug accumulation and auto-inhibition of CYP3A4. Letrozole exposure (C_{max} and $AUC_{0–24h}$; Table 1-3) on C1D21 was similar to or slightly lower than previously reported in studies with letrozole. Variability in attainment of steady-state for letrozole (2–6 weeks) could account for differences. Letrozole accumulation was 5.2-fold following multiple doses, consistent with the long half-life reported for letrozole (≈2 days).

Table 1-3 PK Parameters of ribociclib and letrozole in all patients (N=47)

Analyte	Day	T_{max} (h)*	C_{max} (ng/mL)†	AUC_{0-24} (h.ng/mL)†	R_{acc}†	$T_{1/2, acc}$ (h)†	CL/F (L/h)†
Ribociclib	C1D1	2.1 (1.0-4.2) [41]	1130 ± 486 [41]	10900 ± 3750 [37]	-	-	-
	C1D21	2.1 (1.0-7.7) [28]	1870 ± 750 [28]	25900 ± 11 600 [23]	2.4 ± 0.8 [19]	32.5 ± 12.5 [18]	30.1 ± 17 [20]
Letrozole	C1D1	2.0 (0.5-8.0) [42]	25.7 ± 13 [42]	378 ± 297 [38]	-	-	-
	C1D21	2.0 (0.7-8.0) [34]	93.4 ± 36 [34]	1840 ± 827 [31]	5.2 ± 2.2 [24]	77.3 ± 36.6 [24]	1.7 ± 0.8 [29]

AUC0–24h, area under curve between 0 and 24 hours; C, Cycle; CL/F, apparent oral clearance of drug; Cmax, maximum plasma concentration; D, Day; pts, patients; Racc, accumulation ratio; SD, standard deviation; T1/2, acc, elimination half-life; Tmax, time to reach maximum plasma concentration. *Mean (range) [n]. †Mean ± SD [n].
Data cut-off: October 30, 2015.

Of the 47 pts evaluable for response per RECIST v1.1, one complete response (CR; treatment-naïve group) was observed. In the previously treated group, 1 pt (5%) had a confirmed partial response (PR), 7 pts (37%) had neither complete response nor progressive disease (NCRNPD; non-measurable disease), 7 pts (37%) had stable disease (SD;

measurable disease), and 4 pts (21%) had progressive disease (PD). A summary of best overall responses for pts in the treatment-naïve group is shown in Table 1-4. As of the October 30, 2015 data cut-off date, the median PFS in the treatment-naïve group had not been reached; pts are being monitored for disease progression.

As of August 19, 2016, 47 patients had been treated with ribociclib 600 mg QD (3-weeks-on/1-week-off) + letrozole 2.5 mg QD (continuous; Table 1).Table 1-1). 17 of 19 patients (89%) in dose escalation were previously treated for aBC (previously treated group). 27 of 28 patients (96%) in dose expansion were treatment-naïve for aBC (first-line group).

Treatment has been discontinued in all 19 patients in the previously treated group (100%) and 15 patients (54%) in the first-line group.

Median progression-free survival (PFS) in the first-line group was 25.3 months; 11 patients had disease progression and 17 patients were censored at the data cut-off date, with 13 patients still ongoing for further PFS follow up.

Two complete responses (CRs) were observed in the first-line group; overall response rate was 46% and clinical benefit rate was 79%.

Median PFS in the previously treated group was 5.5 months (95% confidence interval: 2.3–8.1); 14 patients had disease progression and 5 patients were censored at the data cut-off date, with no patients ongoing for further PFS follow-up. (Munster et al. presented at SABCS, San Antonio, TX, 6–10 December 2016, Abstract P-4-22-18).

Table 1-4 Summary of best overall response for the treatment-naive group per investigator assessment

	Treatment-naïve Group	
	All Pts (N=28)	Pts With Measurable Disease (n=24)
Best overall response, n (%)		
CR	1(4)	1 (4)
PR	10 (36)	10 (42)
SD	10 (36)	10 (42)
PD	3 (11)	3 (13)
NCRNPD	4 (14)	-
Objective response rate (confirmed CR + PR), % (95% CI)	39 (22-59)	46 (26-67)
Disease control rate (confirmed CR + PR + SD + NCRNPD), % (95% CI)	89 (72-98)	88 (68-97)
Clinical benefit rate (confirmed CR + PR + SD >24 weeks + NCRNPD >24 weeks), % (95% CI)	79 (59-92)	79 (58-93)

CI, confidence interval; CR, complete response; NCRNPD, neither complete response nor progressive disease (non-measurable disease); PD, progressive disease; PR, partial response; pts, patients; SD, stable disease.
Data cut-off: October 30, 2015.

In summary, ribociclib in combination with letrozole demonstrated encouraging clinical activity, particularly in the ongoing treatment-naïve group (46% objective response rate, 88% disease control rate, 79% clinical benefit rate in pts with measurable disease). The combination of ribociclib and letrozole has an acceptable safety profile in pts with ERpos, HER2neg aBC. Neutropenia observed with ribociclib is an on-target, antiproliferative side effect of CDK4/6 inhibition. AEs were generally tolerable and managed through dose reductions and interruptions. (Juric et al. Presented at ASCO Annual Meeting, Chicago, IL,

3–7 June 2016, Abstract 568; Munster et al. presented at SABCS, San Antonio, TX, 6–10 December 2016, Abstract P-4-22-18).

Additionally, the ongoing Phase III MONALEESA-2 study (CLEE011A2301) of ribociclib in combination with letrozole for the first-line treatment of postmenopausal women with HR+, HER2-negative advanced (metastatic or loco regionally recurrent) breast cancer, which has completed enrollment (NCT01958021), met its primary endpoint early at the preplanned interim analysis.. Data analysis has been completed and data have been published in October 2016:

Ribociclib in combination with letrozole demonstrated statistically significant benefit over placebo in combination with letrozole in prolonging PFS based on Investigator assessment. Clinical benefit was evident relative to placebo plus letrozole with a 44.4% estimated risk reduction in the primary PFS endpoint as per Investigator assessment (HR=0.556, 95% CI: 0.429, 0.720; p=3.29×10-6).

As of 5 Mar 2015, 668 patients were randomized; 334 patients each to the ribociclib plus letrozole arm and the placebo plus letrozole arm. The median studyy follow-up was 15.3 months, as of the 29-Jan-2016 data cut-off date, and the proportion of patients continuing to receive treatment in the ribociclib plus letrozole arm was higher than in placebo plus letrozole arm (58.4% vs 46.1%, respectively). Disease progression was the primary reason for treatment discontinuation and was more frequent in the placebo plus letrozole arm compared to the ribociclib plus letrozole arm (43.7% vs. 26%). Adverse events led to the discontinuation of study treatment in 32 patients (4.8%): 25 patients (7.5%) in ribociclib plus letrozole arm and seven patients (2.1%) in placebo plus letrozole arm.

The median age of patients was 62 years (range: 23-91) and 44.2% were of ≥ 65 years old. The majority of the patients were Caucasian (82.2%). All patients had ECOG performance status of either 0 or 1. Approximately one-third (34.0%) of the patients in this study were de novo breast cancer patients. Nearly two-thirds (58.8%) of patients had visceral disease (19.8% with liver and 45.4% with lung involvement) and 22.0% had bone only metastases at study entry. All except four patients had stage IV disease at the time of study entry (other four had stage III disease). One-third (34.0%) of the patients had ≥ 3 metastatic sites.

The median duration of exposure to study treatment was 13.0 months in the ribociclib arm and 12.4 months in the placebo arm. The median duration of exposure to ribociclib/ placebo was 12.2 months in the ribociclib arm and 12.4 months in the placebo arm; 240 patients (71.9%) were exposed to ribociclib plus letrozole therapy for ≥ 9 months. Median relative dose intensity was 87.5% for ribociclib and 100% for placebo. Ribociclib dose interruptions occurred in 257 (76.9%) patients, and letrozole was interrupted in 132 (39.5%) patients in the ribociclib arm. Placebo was interrupted in 134 (40.6%) patients and letrozole was interrupted in 107 (32.4%) patients in the placebo arm. Dose reductions occurred in 53.9% and 7.0% of patients in the ribociclib and placebo arms, respectively, most commonly for adverse events (169 [50.6%] vs. 14 [4.2%] patients; ribociclib vs. placebo arm). Dose reduction due to neutropenia occurred in 65% of patients who had a dose reduction due to AEs in the ribociclib arm.

Majority of the patients experienced at least one AE in both treatment groups (98.5% vs.97%); the most commonly (≥ 30%) reported AEs in ribociclib plus letrozole group irrespective of causality were: neutropenia (60.8%), nausea (51.5%), fatigue (36.5%), diarrhea (35%), and alopecia (33.2%). AEs where a higher proportion of ribociclib plus letrozole-treated patients reported events (and where there was a ≥ 10% difference to the placebo plus letrozole group) included neutropenia (+56.6%), nausea (+23%), decreased neutrophil count (+18%), alopecia (+17.7%), decreased white blood cell count (+17.4%), vomiting (+13.8%), anemia (+13.8%), diarrhea (+12.9%), leukopenia (+12.9%), increased ALT (+11.7%), and increased AST (+11.4%). The incidence of SAEs was 21.3% and 11.8% in the ribociclib plus letrozole and placebo plus letrozole arms, respectively. Twenty-five patients (7.5%) from the ribociclib plus letrozole group experienced SAEs that were considered by the Investigator to be related to study treatment. Febrile neutropenia was the only suspected SAE reported in >1% of patients (1.2%). Permanent discontinuations due to adverse events was reported in 7.5% of patients receiving ribociclib plus letrozole and 2.1% in patients receiving placebo plus letrozole. The most common AEs leading to treatment discontinuation of both ribociclib and letrozole were ALT increased (2.7%), AST increased (2.4%) and vomiting (1.5%).

Neutropenia, QT prolongation and hepatobiliary toxicity are important identified risks with ribociclib treatment:

- Neutropenia, irrespective of causality, was the most common adverse event in the ribociclib plus letrozole arm. All grade neutropenia occurred in 60.8% of patients, with grade 3 neutropenia in 39.5% and grade 4 in 8.7% of patients. There were five (1.5%) cases of febrile neutropenia.
- Grade 3 or 4 increases in ALT (10.2% vs. 1.2%) and AST (6.9% vs. 1.5%) were reported in the ribociclib plus letrozole and placebo plus letrozole arms respectively. Four patients met the criteria for Hy's Law in ribociclib plus letrozole group, 3 of these cases were confirmed with biopsies. All liver function test elevations in these patients were reversible and returned to normal values after stopping ribociclib.
- There were 11 patients (3.3%) with a new QTcF >480 ms post-baseline (average of triplicate QTcF) and 9 (2.7%) with a >60 ms increase from baseline in the ribociclib plus letrozole group (six out of 11 patients who had new QTcF 480 ms plus three others).

There were 4 deaths (3 [0.9%] in the ribociclib group and 1 (0.3%) in the placebo group). One patient in each group died from the progression of underlying breast cancer. The remaining 2 deaths in the ribociclib group were due to sudden death and death from an unknown cause. The case of sudden death was considered to be related to ribociclib and occurred on day 11 in cycle 2 in association with grade 3 hypokalemia (treated with oral potassium supplements) and a grade 2 prolongation in the QTcF interval on day 1 of cycle2. The patient who died from an unknown cause received ribociclib for 4 days before withdrawing consent and discontinuing the study treatment; her death was reported 19 days later and was not considered to be related to ribociclib by the investigator.

Key efficacy results:

Study A23301 met its primary objective at the primary analysis, with compelling evidence of clinical benefit in patients with HR-positive, HER2-negative advanced breast cancer. A 44.4% estimated risk reduction in ribociclib plus letrozole treated patients was evident in

the primary PFS endpoint as per investigator assessment (HR=0.556, 95% CI: 0.429, 0.720; one sided p- value $=3.29\times10^{-6}$). Results were consistent across the subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, bone only metastasis disease.

Overall survival data were immature at the time of this interim analysis with 43 deaths being reported (23 patients [6.9%] and 20 patients [6.0%], respectively), from the ribociclib plus letrozole and placebo plus letrozole treatment arms.

Improved ORR of 40.7% versus 27.5% and CBR of 79.6% vs 72.8% were reported for the ribociclib plus letrozole arm relative to placebo plus letrozole arm, supporting the primary endpoint of efficacy of ribociclib plus letrozole over placebo plus letrozole. The median time to response and duration of response were not achieved in either treatment arms. The ORR (52.7% vs. 37.1%) and CBR (80.1% vs. 71.8%) in the subgroup of patients with measurable disease at baseline were consistent with the primary analysis results.

Table 1-5 Adverse events with suspected relationship to study treatment in study (CLEE011A2301)

Adverse events with suspected relationship to study treatment by preferred term and maximum grade (greater 5% in either arm) (Safety set)	Ribociclib + Letrozole n=334			Placebo + Letrozole n= 330		
Preferred Term	All grades (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Total	319 (95.5)	199 (59.6)	43 (12.9)	249 (75.5)	27 (8.2)	1 (0.3)
Neutropenia	199 (59.6)	130 (38.9)	29 (8.7)	13 (3.9)	2 (0.6)	0
Nausea	144 (43.1)	6 (1.8)	0	54 (16.4)	0	0
Alopecia	95 (28.4)	0	0	44 (13.3)	0	0
Fatigue	92 (27.5)	5 (1.5)	1 (0.3)	64 (19.4)	2 (0.6)	0
Diarrhea	72 (21.6)	3 (0.9)	0	39 (11.8)	0	0
Neutrophil count decreased	63 (18.9)	44 (13.2)	3 (0.9)	3 (0.9)	1 (0.3)	0
Vomiting	62 (18.9)	6 (1.8)	0	22 (6.7)	1 (0.3)	0
White blood cell count decreased	57 (17.1)	37 (1.1)	2 (0.6)	5 (1.5)	1 (0.3)	0
Hot flush	51 (15.3)	1 (0.3)	0	63 (19.1)	0	0
Arthralgia	48 (14.4)	1 (0.3)	0	52 (15.8)	1 (0.3)	0
Leukopenia	48 (14.4)	25 (7.5)	1 (0.3)	9 (2.7)	1 (0.3)	0
Anemia	46 (13.8)	2 (0.6)	0	9 (2.7)	3 (0.9)	0
Rash	45 (13.5)	2 (0.6)	0	10 (3.0)	0	0
Alanine aminotransferase increased	42 (12.6)	22 (6.6)	5 (1.5)	8 (2.4)	1 (0.3)	0
Constipation	40 (12.0)	0	0	20 (6.1)	0	0
Decreased appetite	39 (11.7)	3 (0.9)	0	18 (5.5)	0	0
Aspartate aminotransferase increased	36 (10.8)	12 (3.6)	2 (0.6)	8 (2.4)	3 (0.9)	0
Stomatitis	33 (9.9)	1 (0.3)	0	15 (4.5)	0	0
Pruritus	30 (9.0)	1 (0.3)	0	3 (0.9)	0	0
Asthenia	27 (8.1)	1 (0.3)	0	23 (7.0)	1 (0.3)	0
Headache	27 (8.1)	1 (0.3)	0	24 (7.3)	0	0
Dysgeusia	23 (6.9)	0	0	12 (3.6)	0	0
Dry mouth	21 (6.3)	1 (0.3)	0	14 (4.2)	0	0
Dizziness	19 (5.7)	0	0	21 (6.4)	0	0
Thrombocytopenia	19 (5.7)	1 (0.3)	0	0	0	0
Lymphocyte count decreased	18 (5.4)	12 (3.6)	0	3 (0.9)	2 (0.6)	0

The ongoing phase III study MONALEESA-3 (CLEE011F2301) investigates ribociclib in combination with the selective estrogen receptor degrader fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.
Premenopausal patients are currently investigated in the ongoing phase III study MONALEESA-7 (CLEE011E2301), which is a randomized, double-blind, placebo-controlled
study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of women with hormone receptor positive, HER2-negative, advanced breast cancer.
Results for both phase III trials are expected to be available in 2017.

2 Rationale

2.1 Study rationale and purpose

In international guidelines for advanced breast cancer, endocrine treatment is the preferred treatment option for premenopausal and postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer, unless there is concern or proof of endocrine resistance or rapidly progressive disease requiring a fast response (Cardoso 2012).
Multiple pathways are known in which alterations can facilitate endocrine resistance. Two related emerging mechanisms of endocrine resistance include the decoupling of cell cycle control from ER-signaling and the utilization of alternate growth signaling pathways such as the PI3K pathway (Miller et al 2011; Lange and Yee 2011). The currently available standard option for overcoming endocrine resistance targets the PI3K/AKT/mTOR pathway as well as the estrogen receptor pathway by combining the mTOR inhibitor Afinitor (everolimus) with the steroidal aromatase inhibitor exemestane. This combination demonstrated superior efficacy with a manageable safety profile compared to exemestane monotherapy. The median progression free survival in the pivotal phase III trial BOLERO-2 was 7,8 months for the combination of everolimus plus exemestane versus 3.2 months for exemestane and placebo (hazard ratio = 0.45; 95% confidence interval 0.38–0.54); log-rank P<0.0001) (Yardley 2013).
Besides the PI3K/AKT/mTOR pathway, one of the most frequently altered pathways in breast cancer is the cell cycle regulation by cyclin D1 and cyclin dependent kinases 4 and 6. By targeting two distinct pathways (aromatase inhibition by letrozole, CDK4/6 pathway inhibition by ribociclib), it is hypothesized that this combination will result in prolonged progression free survival. First clinical results demonstrated promising efficacy and safety data in a Phase Ib trial (CLEE011X2107). In this study, ribociclib in combination with letrozole demonstrated encouraging clinical activity, in both the treatment-naïve group (46% objective response rate, 88% disease control rate, 79% clinical benefit rate in pts with measurable disease) as well as pretreated patients (1 pt (5%) had a confirmed PR, 7 pts (37%) had NCRNPD (non-measurable disease), 7 pts (37%) had SD (measurable disease), and 4 pts (21%) had PD).The most common adverse events suspected to be study drug related were Neutropenia (70% all grades, 43% grade 3/4), Nausea (43% all grades, no grade 3/4), Fatigue (26% all grades, no grade 3/4), Alopecia, Anemia and Diarrhea (23% all grades, no grade 3/4, respectively).

MonaLEEsa-2 (CLEE011A2301) is the fully recruited, ongoing placebo controlled phase III study of ribociclib in combination with letrozole in postmenopausal woman which has shown to prolong PFS in patients with HR+ and HER2- advanced breast cancer who received no prior therapy for advanced disease. The study has met its primary endpoint, progression-free survival using RECIST 1.1 criteria, in a preplanned interim analysis as recommended by an independent data monitoring committee. The interim analysis allowed stopping the study for outstanding efficacy for the ribociclib containing therapy arm. The statistical analysis was performed by an independent statistician (not involved with the conduct of the study). The results of this interim analysis will be reported later this year.
Ribociclib in combination with aromatase inhibitor therapy and goserelin is currently investigated in premenopausal patients in the phase III trial MonaLEEsa-7 (CLEE011F2301). Paloma-3, a phase III trial with a different CDK4/6 inhibitor in combination with fulvestrant, demonstrated equal efficacy in premenopausal patients and postmenopausal patients. Premenopausal patients in this trial also received goserelin in addition to the CDK4/6 inhibitor and fulvestrant.
To support the encouraging results of MonaLEEsa-2, the main purpose of this study is to collect additional efficacy and safety data for the combination of ribociclib and letrozole in a patient population additional to the MonaLEEsa-2 study and to provide access to ribociclib to patients for which available treatment options are not satisfactory treatment alternatives until the drug is approved for this indication. Furthermore, this trial aims to collect data for the combination of ribociclib and letrozole in the context of current local routine therapy algorithms for the treatment of metastatic and advanced breast cancer.
Preclinical and early clinical data suggests that CDK4/6 inhibition may play a key role in the treatment of subsets of breast cancer by abrogating endocrine-resistant cell proliferation. Therefore, the addition of a CDK4/6 inhibitor such as ribociclib to standard endocrine therapy (letrozole or letrozole and goserelin for premenopausal patients, respectively) is a promising therapeutic approach that will be explored in this study. Letrozole is the AI that will serve as endocrine combination partner in this study. It has been extensively studied in the postmenopausal setting and was chosen as endocrine combination partner in the pivotal phase III trial MonaLEEsa-2.
The present multi-center, open-label, single-arm study aims to evaluate the efficacy and safety, and quality of life for the combination of ribociclib and letrozole in a patient population additional to the MonaLEEsa-2 study, i.e. in patients pretreated with one line of chemotherapy and/or a maximum of two lines of endocrine therapy as well as premenopausal patients, without limitations regarding the disease free interval after adjuvant therapy. The exploratory objectives of this study are hypothesis generating and will cover analyses of crucial scientific interest.

Since the combination was shown to significantly improve PFS in the MonaLEEsa-2 trial, for ethical reasons no endocrine comparator drugs will be investigated in the present study. The duration of study treatment of 80 weeks is adequate to determine the primary, secondary and exploratory study parameters. The sample size is suitable to estimate the CBR in this patient population with reasonable precision.

2.2 Rationale for the study design

Current treatment options for advanced HRpos/HER2neg breast cancer delay tumor progression, but ultimately lead to a relapse. Therefore new treatment options are needed to better control tumor growth. The phase III MonaLEEsa-2 trial demonstrated significant efficacy for the combination treatment of ribociclib and letrozole compared to letrozole

monotherapy in advanced HRpos/HER2neg breast cancer patients who were naïve to prior treatment for the metastatic setting at the preplanned interim analysis.

The present national, multi-center, open-label, single-arm study aims to evaluate the efficacy, safety and quality of life of the combination of ribociclib and letrozole in an additional patient population compared to MONALEESA-2, for which existing treatment options are not satisfactory treatment alternatives, i.e. with fewer restrictions regarding prior therapies for the advanced setting (up to one prior chemotherapy allowed, up to two lines of prior endocrine therapy allowed, premenopausal patients allowed, men allowed). The exploratory objectives of this study are hypothesis generating and will cover analyses of crucial scientific interest, [redacted]

Since the combination was shown to significantly improve PFS in the previous MonaLEEsa-2 trial, for ethical reasons no endocrine comparator drugs will be investigated in the present study. The sample size is suitable to estimate the CBR in this patient population with reasonable precision.

Ribociclib and letrozole (and goserelin) will be provided by the sponsor to all patients who were enrolled prior to commercial availability of ribociclib. Patients who were enrolled into the study after commercial availability of the trial and are treated according to the SmPC will receive commercial drug (ribociclib + letrozole). All patients who are treated outside of the label of the SmPC will still be supplied with ribociclib and letrozole within the trial.

2.3 Rationale for dose and regimen selection

The dose of ribociclib is 600 mg daily orally for 21 days, followed by 7 without taking ribociclib. The recommended daily dose of Letrozole is 2.5 mg via oral administration continuously.

Both drugs were shown to be safe and effective in the respective dose and regimens. The recommended dose for goserelin is 3,6 mg administered as subcutaneous implant once a month.

2.4 Rationale for choice of combination drugs

In this study ribociclib will be administered in combination with letrozole, which is a non-steroidal aromatase inhibitor that has demonstrated efficacy in the treatment of postmenopausal patients with ABC/MBC.

Letrozole is indicated for the following patient populations:

- Adjuvant treatment of postmenopausal women with hormone receptor positive (HRpos) early BC.
- Extended adjuvant treatment of early breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy.
- First-line treatment of postmenopausal women with HRpos or hormone receptor unknown locally advanced or metastatic breast cancer.

Advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy or whose disease has progressed following antiestrogen therapy.

Preliminary PK data for the combination of ribociclib (600 mg) and letrozole (2.5 mg) indicate that ribociclib and letrozole exposures are within the range of values for the respective single agent and the combination is safe and tolerable.

In study CLEE011X2107, ribociclib in combination with letrozole demonstrated encouraging clinical activity, particularly in the treatment-naïve group (46% objective response rate,

89% disease control rate, 79% clinical benefit rate in pts with measurable disease). The combination of ribociclib and letrozole has an acceptable safety profile in pts with ERpos, HER2neg aBC. Neutropenia observed with ribociclib is an on-target, antiproliferative side effect of CDK4/6 inhibition. AEs were generally tolerable and managed through dose reductions and interruptions. (Munster et al. presented at SABCS, San Antonio, TX, 6–10 December 2016, Abstract P-4-22-18).

Recently, the MONALEESA-2 trial reported a significant benefit for hormone receptor positive HER2-negative postmenopausal women who were naïve to treatment for advanced breast cancer by combining ribociclib (LEE011) with letrozole. In this randomized, double blind, placebo-controlled trial a statistically significant improvement in progression-free survival (PFS) by adding ribociclib to letrozole versus letrozole alone was reported.

Premenopausal patients in this study will be administered goserelin in addition to ribociclib and letrozole. Estrogen deprivation therapy is the core treatment modality in patients with ER+ advanced breast cancer. Endocrine therapy options for premenopausal women with ER+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer) include selective ER modulators (SERM; e.g. tamoxifen, raloxifene), and luteinizing hormone-releasing hormone agonists (LHRHa; e.g. goserelin). Blocking estrogen signaling with tamoxifen has been the main approach in treatment for premenopausal women with ER+ breast cancer for over 35 years. Current guidelines also recommend treating premenopausal women with advanced HR+ breast cancer with an ovarian function suppression treatment and following treatment recommendations for post-menopausal women, such as non-steroidal AIs (NCCN breast cancer guidelines version 3.2014).

Ovarian suppression of estrogen release with LHRH agonists such as goserelin is effective in preventing relapse in premenopausal women with early stage ER+ breast cancer (Klijn 2001).

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
• The primary objective of this study is the assessment of the clinical benefit rate for the total population and for cohorts A and B separately: o To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole among postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no prior treatment for advanced disease. (70% group) o To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole and goserelin among pre-, and perimenopausal women who received no prior treatment for advanced disease as well as pre-, peri- and postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no more than 1 prior chemotherapy and 2 prior lines of endocrine therapy for advanced disease (30% group)	Clinical Benefit Rate (CBR) after 24 weeks of treatment as defined by RECIST 1.1 as percentage of patients with CR, PR or SD lasting 24 weeks or longer as well as patients with NCRNPD >24 for patients with non-measurable disease	

Objective	Endpoint	Analysis
Secondary		Refer to Section 10.5.1
• To assess the clinical benefit rate (CBR) after 24 weeks among pre- and perimenopausal women without prior therapy for advanced disease • To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib among pre-, peri- and postmenopausal women and men who were pretreated for advanced disease	Clinical Benefit Rate (CBR) after 24 weeks of treatment as defined by RECIST 1.1 as percentage of patients with CR, PR or SD lasting 24 weeks or longer as well as patients with NCRNPD >24 for patients with non-measurable disease	
• Progression-free survival (PFS) for the three different populations (postmenopausal women and men without prior treatment for advanced disease, pre- or perimenopausal women without prior treatment for advanced disease, pre-, peri-, or postmenopausal women and men pretreated for advanced disease)	PFS based on radiologic assessment by investigator using RECIST 1.1 criteria (e.g. mPFS, PFS rate at 12 and 18 months)	
• Overall survival (OS) for the three different populations, defined as the time from date of start of treatment to date of death due to any cause. • Overall response rate (ORR) for the three different populations, defined as complete response or partial response as defined by RECIST 1.1 • To evaluate the safety and tolerability of ribociclib in combination with letrozole (and goserelin in premenopausal patients) • To evaluate patient reported outcomes for health related quality of life	Overall survival (OS) (e.g. OS rate at 12 and 24 months) Overall Response Rate (ORR) after 24 weeks Frequency/severity of AEs and laboratory values	

Objective	Endpoint	Analysis
	Time to 10% deterioration in the global health status/QOL scale score of the EORTC QLQ-C30 Change from baseline in the global health status/QOL scale score of the EORTC QLQ-C30	
Exploratory		Refer to Section 10.6
[redacted]	Analysis methods and endpoints will be used that resemble the current scientific standard at the time of analysis. Such analyses will be described in a separate analysis plan	

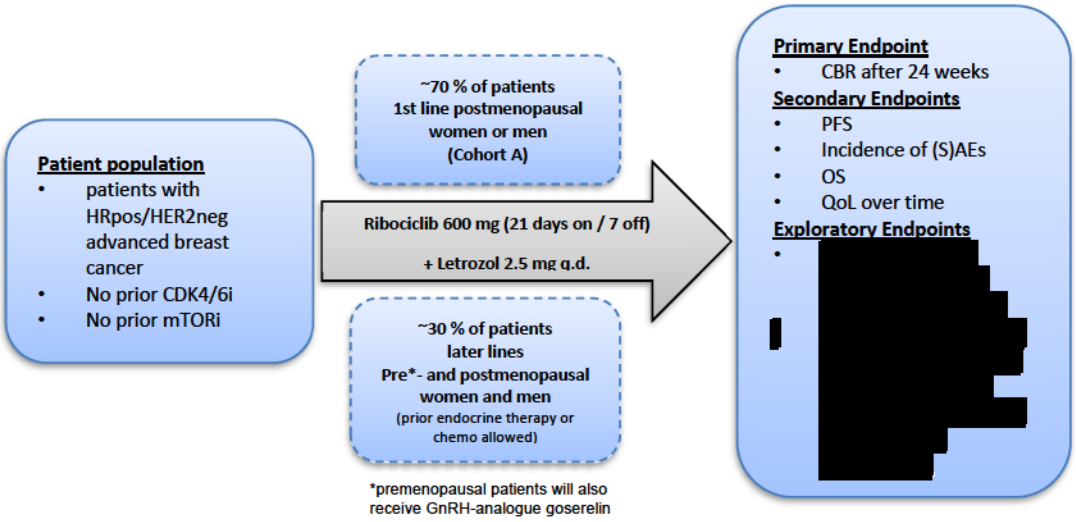
4 Study design

4.1 Description of study design

This is a national, multi-center, open-label, phase IIIb trial to determine the efficacy and safety of treatment with ribociclib (LEE011) plus letrozole in patients with HR+, HER2-negative advanced (recurrent or metastatic) breast cancer.

In this trial a total of 500 patients from approx. 100 centers will be recruited.

Figure 4-1 Study design



The study is sub-divided in the following periods:

Once the Patient Informed Consent Form has been signed and eligibility is confirmed (all inclusion/exclusion criteria have been verified), the patient can be enrolled. All screening evaluations should be performed within 21 days prior to treatment Day 1.

Patients will be treated with daily doses of 600 mg ribociclib (3-weeks-on/1-week-off schedule) in combination with 2.5 mg letrozole daily (continuous dosing). Dose adjustments (dose reduction or interruption) according to safety findings will be allowed. During the study, visits will be performed at baseline, cycle 1 on day 1 & 15 and cycles 2-EOT on day 1. Study treatment will continue until progression, unacceptable toxicity, withdrawal of consent or 80 weeks after the last patient has been enrolled in the trial, whichever comes first.

Novartis will provide ribociclib and letrozole (and goserelin for premenopausal patients) for all patients who are enrolled prior to commercial availability of ribociclib. For patients enrolled afterwards within the approved indication according to SmPC, the investigator will prescribe both ribociclib and letrozole after evaluation of the individual medical patient need for the treatment with ribociclib and letrozole. Patients who are enrolled outside of the label according to SmPC will be provided with study drug by Novartis (i.e. patients in cohort B).

Further treatment after progression will be at the investigator's discretion. Tumor evaluations through CT will be performed for Screening and every 12 weeks during the

study as well as for End of treatment, in case progression as measured by CT was not the reason for end of the treatment.

Patients will be followed up for safety for 30 days after the last dose of study drug. AEs/SAEs with a suspected causality to the study drug must be reported beyond this 30 days safety interval.

4.2 Timing of interim analyses

Three interim analyses are planned during the study. The first interim analysis will be conducted one year after the first patient has been enrolled and include a preliminary analysis on safety. The second interim analysis will be conducted 12 months after LPFV in the 30% pretreated and premenopausal cohort and will include a preliminary analysis on safety, efficacy and quality of life. The third interim analysis will take place 6 months after the last patient has been recruited and will include a preliminary analysis on safety and efficacy.

4.3 Definition of end of the study

The end of treatment (LPLT=EOT) for all patients is planned80 weeks after recruitment of the last patient (LPFT) or progression of disease of of all patients, whichever occurs first. Based on the data of the Monaleesa-2 study and the interim analysis, observation time might be adjusted in order to achieve median PFS.

Patients will be followed for safety for 30 days after the individually last dose of study drug to achieve the end of study (LPLV). After last patient last treatment (LPLT), the post-antineoplastic treatment, the current progression and survival status for all patients will be updated finally and recorded in the eCRF.

4.4 Early study termination

Novartis and the study steering committee can decide to terminate the study early, e.g. for changes in Risk-Benefit-Ratio or Futility. Additionally, Novartis can terminate the study for reasons stipulated in the clinical trial agreement. Should this be necessary, the patient should be seen as soon as possible for the final visit and the same assessments should be performed as described in Table 7-1 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. Novartis will be responsible for informing the ethics committee of the early termination of the trial.

5 Population

5.1 Patient population

This study will be performed in 500 patients with hormone receptor positive locally advanced or metastatic breast cancer as defined by:

- Cohort A: approx. 70% of patients must be postmenopausal women or men without any treatment for advanced disease.
- Cohort B: approx. 30% of patients can be pre- or perimenopausal women or postmenopausal women or men, must have no more than 1 chemotherapy line for advanced disease, and maximum 2 lines of endocrine therapy for advanced disease (or a combination of these criteria).

When the number of patients for one of the cohorts is reached, no more patients will be included in this cohort.

Patients must have documented evidence of recurrence or progression during or after the last therapy prior to enrollment (except for de novo metastasized patients).

Written informed consent must be obtained prior to any screening procedures. Patients incapable of giving consent personally may not be included in this study.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment 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, ≥ 18 years old at the time of informed consent and has signed informed consent before any trial related activities.
2. Women and men with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy.
3. **A) For inclusion in cohort A:** Patient is postmenopausal woman or man. Postmenopausal status is defined either by:
   - Prior bilateral oophorectomy
   - Age ≥60
   - 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

   Note: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy). In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
   Ovarian radiation is not permitted for induction of ovarian suppression in this trial. Patients treated with a luteinizing hormone-releasing hormone agonist (LHRHa) (goserelin acetate) will be enrolled in cohort B.

   B) For cohort B, also premenopausal or perimenopausal patients may be included. Premenopausal status is defined as either:
   - Patient had last menstrual period within the last 12 months,
     OR
   - If on tamoxifen within the past 14 days, plasma estradiol must be ≥10 pg/mL and FSH ≤40IU/l or in the premenopausal range, according to local laboratory definition,
     OR
   - In case of therapy induced amenorrhea, with a plasma estradiol ≥10 pg/mL and/or FSH ≤40IU/l or in the premenopausal range according to local laboratory definition.

4. Patients who have undergone bilateral oophorectomy are considered postmenopausal: Cohort A without pretreatment for advanced or metastatic situation, Cohort B with pretreatment for advanced or metastatic disease.
5. Perimenopausal status is defined as neither premenopausal nor postmenopausal.
6. For premenopausal patients: Confirmed negative serum pregnancy test (β-hCG) before starting study treatment or patient has had a hysterectomy.
7. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory.
8. 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.
9. Patient must have either:
   - Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria
     OR
   - Bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease
     OR
   - Non-measurable disease (including osteoblastic bone lesions)

   Note: Tumor lesions previously irradiated curatively or subjected to other locoregional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented.
10. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 or 2
11. Patient has adequate bone marrow and organ function as defined by 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
    - INR ≤ 1.5
    - Serum creatinine < 1.5 mg/dl or creatinine clearance ≥ 50 mL/min.
    - Total bilirubin $\leq$ ULN except for patients with Gilbert's syndrome (Morbus Meulengracht) who may only be included if the total bilirubin is $\leq 3.0 \times$ ULN or direct bilirubin $\leq 1.5 \times$ ULN.
    - Aspartate transaminase (AST) $< 2.5 \times$ ULN, except for patients with liver metastasis, who are only included if the AST is $< 5 \times$ ULN
    - Alanine transaminase (ALT) $< 2.5 \times$ ULN, except for patients with liver metastasis, who are only included if the ALT is $< 5 \times$ ULN
12. Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication:
    - Sodium
    - Potassium
    - Magnesium
    - Total Calcium (corrected for serum albumin in patients with hypoalbuminemia)
13. Standard 12-lead ECG values assessed by the local laboratory
    - QTcF interval at screening < 450 msec (using Fridericia's correction)

14. Resting heart rate 50-90 bpm

5.3 Exclusion criteria

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

1. Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment.
2. Patient who received any prior CDK4/6 inhibitor
3. Patient who received any prior mTOR-inhibitor
4. Patient has a known hypersensitivity to any of the excipients of ribociclib, letrozole (or goserelin if pre- or perimenopausal)
5. Patients with current inflammatory breast cancer (< 4 weeks before enrollment).
6. **For Cohort A:** prior treatment for advanced or metastatic disease
   - Patients who received ≤ 21 days of aromatase inhibitor treatment for advanced disease prior to enrollment are eligible.

   Note: Patients starting study treatment directly after any endocrine anti-cancer therapy within less than 5 half-lives of the previous therapy should be monitored closely for possible overlapping toxicities.
7. **For Cohort B:**
   - Patient who has received more than one prior chemotherapy regimen for advanced breast cancer
     AND/OR
   - Patient who has received more than two prior hormonal therapy regimens for advanced breast cancer. (Treatment for ≤ 21 days with an aromatase inhibitor for advanced disease is not considered an endocrine therapy line).
8. Patient is concurrently using other anti-cancer therapy. (Treatment with bisphosphonates or denosumab is generally not considered anti-cancer therapy).
9. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects.
10. Patient has not recovered from all toxicities related to prior anticancer therapies to NCI CTCAE version 4.03 Grade ≤1. Exception to this criterion: patients with any grade of alopecia are allowed to enter the study.
11. Patient has a concurrent malignancy or malignancy within 3 years of enrollment, with the exception of adequately treated, basal or squamous cell skin carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
12. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
    - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment.
    - Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
13. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
14. Patient has a known history of HIV infection (testing not mandatory).
15. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks,

contraindicate patient participation in the clinical study or compromise compliance with the protocol: (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial or viral infections, etc.).

16. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, including 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:
        - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia.
        - 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.
        - Inability to determine the QT interval on screening (QTcF, using Fridericia's correction).
        - Systolic blood pressure (SBP) >160 mmHg or <90 mmHg at screening.
17. Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1:
    - Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pomelos, star-fruit, and Seville oranges.
    - That have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
    - Herbal preparations/medications. Dietary supplements are allowed if they contain only nutrients, minerals and/or vitamins.
18. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
    Note: The following uses of corticosteroids are permitted: 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).
19. Participation in a prior investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longer.
20. For premenopausal women: Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
21. 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 of study treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. 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) or tubal ligation at least six 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 sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
- Combination of:
  - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Note: sexually active males should use a condom during intercourse while taking drug and for 21 days after stopping medication and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Study treatment

For this study, the term "investigational drug" refers to Novartis study drug ribociclib (LEE011). The other investigational drugs to be used in this study are letrozole as well as goserelin acetate for pre-and perimenopausal women; men may also be treated with goserelin acetate at the discretion of the investigator. Study treatment in this study refers to the combination of drugs and includes investigational drug (ribociclib) as well as letrozole and goserelin acetate.

Novartis will provide ribociclib and letrozole (and goserelin) for all patients who are enrolled prior to commercial availability of ribociclib. For patients enrolled afterwards within the approved indication according to SmPC, the investigator will prescribe both ribociclib and letrozole after evaluation of the individual medical patient need for the treatment with ribociclib and letrozole. Patients who are enrolled outside of the label according to SmPC will be provided with study drug by Novartis (i.e. patients in cohort B).

Patients enrolled after commercial availability of ribociclib and letrozole, who are to be treated within the label and are covered by private health insurance should contact their private health insurance to ensure that the insurance will cover the costs of the prescription.

Ribociclib will be supplied by Novartis or its designee as 200 mg film-coated tablets as individual patient supply packaged in bottles or blisters. Letrozole and goserelin acetate will be procured locally as it is commercially available in Germany. Storage conditions are described in the medication label.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. On the first day of each cycle, patients will receive an adequate drug supply (before commercial availability) or a prescription (after commercial availability) for self-administration at home.

The investigator must emphasize compliance and will instruct the patient to take ribociclib (LEE011) and letrozole as well as goserelin exactly as prescribed.

6.1.1 Dosing regimen

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 (3x200mg)	Once daily - Days 1-21 of each 28 day cycle
Letrozole	Tablet for oral use	2.5 mg	Once daily
Goserelin (for premenopausal patients)	Subcutaneous implant	3.6mg	Day 1 of each cycle

Ribociclib will be given orally once a day on days 1-21 of each 28 day cycle. Days 22-28 will be a "rest" from ribociclib. Letrozole will be given every day. Goserelin will be injected monthly for pre- or perimenopausal patients only.

Ribociclib, letrozole and goserelin will be administered as a flat-fixed dose, and not by body weight or body surface area.

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

6.1.1.1 Ribociclib dosing

Ribociclib 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 drug combination of ribociclib and letrozole with a large glass of water (~250 mL) at the same time each day. Evening doses are strongly not recommended.
- Ribociclib can be administered with or without food; however dietary habits around the time of dosing should be as consistent as possible throughout the study.
- Patients should be instructed to swallow the ribociclib whole and not to chew or crush them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.

- Patients must avoid consumption of grapefruit, grapefruit hybrids, pomelos, 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 medications, due to potential CYP3A4 interaction with the study medications.

Note: Orange juice is allowed.

1. Herbal or dietary supplements known as strong inhibitors or inducers of CYP3A4 or those with a known risk of QT prolongation are not permitted.

   .
2. Multivitamins are permitted.

6.1.1.2 Additional dosing guidelines for ECG/Chemistry panel/Lipid Panel collection

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

- On a day of chemistry panel, hepatic safety markers and/or lipid panel sampling, patients must be fasting from all food and drink for at least **8** hours overnight. Water is allowed during all fasting periods; however coffee, tea and juice are not permitted during the fasting period. Patients must also take study treatment in the clinic under the supervision of the Investigator or designee. On all other days patients may take the study treatment at home.
- If a pre-dose ECG measurement should be collected, then the ECG measurement should occur before dosing of the study treatment

6.1.2 Treatment duration

Patient may continue treatment with the study drug until patient experiences unacceptable toxicity, disease progression (any radiologic according to RECIST 1.1) and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent must be documented accordingly.

[redacted] Study drug interruption refers to a patient stopping either study drug during the course of the study, but then re-starting it at a later time in the study. If one of the study drugs is discontinued, the other must be discontinued as well. If the study drug ribociclib or letrozol is interrupted for more than 4 weeks, the patient will be permanently discontinued from the study treatment.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied:

Table 6-2 Dose Modification guidelines

	Ribociclib	
	Dose	Number of tablets & 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

These changes must be recorded on the Dosage Administration Record CRF.

6.2.1.1 Ribociclib

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 and Table 6-6.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. However, for events requiring a discontinuation in Table 6-3, Table 6-4, Table 6-5 and Table 6-6 or listed in Section 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 not be adjusted.

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

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.

Toxicity/Grade	Dose Adjustment and Management Recommendations
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. For Grade 3 neutropenia without fever or signs of infection on Day 14 of the first 2 cycles: Consider to continue ribociclib at current dose level to complete cycle. Repeat complete blood count on Day 21. Consider dose reduction based on the neutropenia recovery (<7 days / > 7 days).
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. If toxicity recurs at grade 4: temporary dose interruption until recovery to ≥1.0 x 10^9/L and reduce ribociclib at the next lower dose level.
Leukocyte count (WBC)	
Grade 1 (<LLN - 3.0 x 10^9/L)	No dose adjustment required.
Grade 2 (<3.0 - 2.0 x 10^9/L)	No dose adjustment required.
Grade 3 (<2.0 - 1.0 x 10^9/L)	Dose interruption until recovery to ≥2.0 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 (<1.0 x 10^9/L)	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: temporary dose interruption until recovery to ≥1.0 x 10^9/L and reduce ribociclib at the next lower dose level.
Febrile neutropenia	
Grade 3 ANC <1.0 x 10^9/L with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than one hour	Dose interruption until improvement of ANC ≥ 1.0 x 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue ribociclib.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.
Anemia (Hemoglobin)	
Grade 1 (≥10.0 – LLN g/dL)	No dose adjustment required.
Grade 2 (≥8.0 – <10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	Dose interruption until recovery to grade ≤ 2. Re-initiate ribociclib at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

Table 6-4 Ribociclib dose adjustment and management recommendation for hepatic toxicities

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 bi-weekly
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 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, discontinue ribociclib
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤ 21 days, 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 > 21 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 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 Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	
AST or ALT	
AST or ALT without bilirubin elevation > 2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 – 72 h later)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly 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.	

6.2.1.2 Additional follow-up for hepatic toxicities

Increase in transaminases combined with total bilirubin (TBIL) increase may be indicative of drug-induced liver injury (DILI), and should be considered as clinically important events. A study with ribociclib in non-cancer patients with varying degrees of hepatic impairment (mild, moderate, severe based on Child-Pugh classification) matched subjects with normal hepatic function was completed (CLEE011A2109). Refer to [Ribociclib Investigators Brochure] for more details.

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], whichever is lower, combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

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

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic or hepatocellular liver injury or mixed type injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing 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 (CK), prothrombin time (PT)/INR and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

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

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

All cases 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 met the definition of SAE (Section 8.2.1), and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.2.1.3 Additional follow-up for QTc prolongation

Table 6-5 Ribociclib dose adjustment and management recommendation for QTc prolongation (CTC AE v4.03)

Grade	Dose Modification
For All Grades	1. Check the quality of the ECG and the QT value and repeat if needed. 2. Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib. Consider collecting a time matched PK sample; record date and time of last study drug intake.
1 QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades". No dose adjustment required.
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 < 481ms, restart LEE011 with dose reduced by 1 dose level. If QTcF ≥ 481 ms recurs, ribociclib should be reduced by 1 dose level. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms.
3 QTcF ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Transmit ECG immediately and confirm prolongation/abnormalities. Perform a repeat ECG within one hour of the first QTcF of ≥ 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 ms. If QTcF returns to < 481 ms, ribociclib will be reduced by 1 dose level. If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue LEE011. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms. If QTcF of ≥ 501 ms recurs, discontinue ribociclib.
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.

6.2.1.4 Guidance for all other adverse reactions

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

Patients who experience renal impairment (not due to other contributing factors) of grade 2 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

For patients taking bisphosphonates, the concomitant use of calcium is allowed for the treatment or prevention of hypocalcemia. Patients experiencing Grade 3/4 hypocalcemia should dose interrupt ribociclib until recovery to grade ≤1 and continue with the same dose level.

For all other adverse events please follow recommendations in Table 6-6.

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

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

6.2.1.4.1 Adjustment of starting dose in special populations

Renal Impairment

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

Patients who experience renal impairment (not due to other contributing factors) of grade 2 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

Renal impairment does not affect letrozole PK in humans (Femara® Prescribing Information Novartis).

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

Hepatic Impairment

A study in non-cancer patients with varying degrees of hepatic impairment (mild, moderate, severe based on Child-Pugh classification) and matched patients with normal hepatic function is ongoing ([CLEE011A2109]). Interim results indicated that the exposure (AUC and C_{max}) of ribociclib was similar between the mild hepatic impairment cohort and the normal cohort, was comparable in the moderate and severe cohorts, and both approximately 30% higher than in the normal cohort.In patients with severe hepatic impairment (Child-Pugh C), systemic exposure and terminal half-life of letrozole was twofold increased compared to healthy subjects. These patients should therefore be monitored closely.

Elderly

Insufficient data is available to provide a specific dosage recommendation in elderly population.

6.2.1.5 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 package insert should be consulted regarding full prescribing information and management of adverse events.

6.2.2 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, e.g., neutropenia, liver toxicity and QT-prolongation are provided in Section 6.2.1. Refer to preclinical toxicity and or clinical data found in the Investigator's Brochure.

6.3 Concomitant medications

6.3.1 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-diarrheal are allowed.

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 30 days before entering the study and during the study until safety follow up must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

6.3.1.1 Bisphosphonates and denosumab

Bisphosphonates and denosumab are generally allowed with the following comments:

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

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

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

6.3.1.2 Corticosteroids

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

- Topical applications (e.g., rash), inhaled sprays (e.g., 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) will be accepted.

6.3.1.3 Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines (Smith 2006).

6.3.1.4 Palliative radiotherapy

Palliative radiation is permitted. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow. Palliative radiated lesions cannot be considered for evaluation of tumor response.

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

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

Refer to the ribociclib Investigators Brochure and letrozole or goserelin acetate package insert and Appendix 14.1. for information on possible interactions with other drugs.

6.3.2 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during combined ribociclib and letrozole treatment 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
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index
- Inhibitors of BSEP (based on in vitro data co-administration with LEE011 may lead to intrahepatic cholestasis)
- Medications that carry a possible risk for QT prolongation

- Sensitive substrates of the renal transporters MATE1/2 and and OCT1/2 (potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements)
- Sensitive substrates of BCRP (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)

6.3.3 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
- Substrates of CYP3A4/5 with a narrow therapeutic index
- Medications with a known risk for QT prolongation and/or TdP
- Other investigational and antineoplastic therapies
- Herbal preparations/medications and dietary supplements that are strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation. These include but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto and ginseng. Patients should stop using these preparations/medications at least 7 days prior to first dose of study treatment.

6.3.4 Drugs with QT prolongation

As far as possible, avoid co-administering medications with a "Known", "Possible" or "Conditional" risk of TdP (qtdrugs.org) or any other medication with the potential to increase the risk of drug-related QT prolongation (e.g. via a potential DDI increasing the exposure of LEE011/ placebo 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, LEE011/placebo must be interrupted. If during the course of the study, concomitant administration of a drug with "Possible risk" or "Conditional risk" of TdP is required, based on the investigator assessment and clinical need, study treatment may be resumed under close clinical and ECG monitoring to ensure patient safety. A list of drugs associated with QT prolongation and/or TdP is available online (www.qtdrugs.org). Medications with a known risk for QT prolongation are prohibited during study treatment.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 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.

6.4.2 Treatment assignment or randomization

The assignment of a patient to a cohort will be coordinated by the sponsor or designated CRO by inclusion fax when all inclusion and exclusion criteria are fulfilled. The C1D1 visit should occur within 3 days after sending the fax.

If one of the cohorts reaches the planned patient number, the inclusion of new patients in this cohort will be stopped and all investigators will be informed accordingly.

6.4.3 Treatment blinding

This is an open label study.

6.5 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 goserelin should be dispensed according to the local prescribing information and practice.

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

All study drugs will be provided by Novartis to the participating sites for all patients enrolled in this study until approval of Ribociclib (see Table 6-1) and will be dispensed by the study center personnel on an outpatient basis. For these patients study drugs will be provided by Novartis throughout the study. After ribociclib is commercially available, the investigator will prescribe all drugs according to the label to all patients who will be enrolled after commercial approval.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Table 6-7 Preparation and dispensing

Study drugs	Dispensing	Preparation
Ribociclib Letrozole	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis.	Not applicable
Goserelin	Monthly subcutaneouos implant	Refer to local product information

6.5.1 Study drug packaging and labeling

Ribociclib is formulated as tablets of 200 mg strength for oral administration. Commercially available ribociclib will be supplied as tablets of 200 mg strength for oral administration in

blisters. Complete guidelines for management and administration of letrozole and goserelin can be found in the package insert. Ribociclib study medication will be packaged into bottlesor blisters. The bottles should be opened only at the time of administration, as the drug is hygroscopic and light sensitive. All bottles will conform to all local regulatory requirements.

6.5.2 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 treatment* should be stored according to the instructions specified on the drug labels and according to instructions in the Investigator's Brochure.

Storage conditions for ribociclib, letrozole and goserelin will be described on the medication label/local package insert. The study drug should be stored in a secure, locked area while under the responsibility of the investigator. An authorized person at the investigator's site throughout the entire study must record receipt and dispensing of supplied study drugs.

As long as the study drugs are supplied by Novartis, they are to be stored between 2°C and 25°C and protect from moisture. The storage temperature must be recorded daily (except weekends and bank holidays) in the temperature log.

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

The investigator and/or study personnel will assess compliance at each patient visit. To accurately determine the patient's drug exposure throughout the study, the following information must be reported on the Drug Administration Record CRF for ribociclib, letrozole and goserelin pages and in the source document.

- Planned dose administration
- Actual total daily dose administered
- Start and end date of drug administration
- Dose change (no or yes)
- Reason for dose change (e.g. adverse event, dosing error, lab test abnormality etc.).

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment of study drugs supplied by Novartis as well as of the prescriptions of ribociclib, letrozole and goserelin after ribociclib becomes commercially available. The investigator will be advised to document the dispensing and return of ribociclib, letrozole and goserelin throughout the entire study in a drug accountability log. The field monitor will review drug accountability during site visits and at the completion of the study. The patient will be advised to complete a study drug diary and present the bottles or blisters at the subsequent study visits and at the time of study drug discontinuation to review compliance and allow the investigator to document in the patient file and complete a drug accountability check.
The patient diary is not regarded as study documentation but is regarded as aid for discussions between investigator and patient.

Patients will be asked to return all unused Novartis-supplied study drugs and packaging on an ongoing basis or at the time of study drug discontinuation.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The drug supply should be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Destruction at the site is allowed only if permitted by local regulations and authorized by Novartis.

6.6 Study drug discontinuation

Study drug interruption refers to a patient stopping either study drug during the course of the study, but then re-starting it at a later time in the study. If one of the study drugs is discontinued, the other must be discontinued as well. If the study drug ribociclib or letrozole is interrupted for more than 4 weeks, the patient will be permanently discontinued from the study treatment.

All study drug interruptions must be recorded on the appropriate Dosage Administration CRF.

Patients whose ribociclib treatment is interrupted due to an adverse event or abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 day intervals, until resolution or stabilization of the event, whichever comes first.

Study drug discontinuation refers to a patient's withdrawal from ribociclib. The reason for discontinuation from treatment must be recorded on the End of treatment CRF.

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

- Adverse Event (including, but not limited to QTcF $\geq$ 501 msec, confirmed at repeated ECG measurements and recurrent after dose adjustment was performed; Documented episode of ventricular tachycardia, or ventricular fibrillation; Complete heart block (Grade III AV block) or Second degree AV block Mobitz type II).
- Physician decision
- Progressive Disease
- Protocol deviation
- Study terminated by sponsor
- Adjustments to study treatment that result in discontinuation.
- Use of prohibited medication. Please refer to Section 6.3.3.

Patients who discontinue ribociclib > 28 days should be scheduled for an End of Treatment Visit, whenever possible, after discontinuing ribociclib, at which time all of the assessments listed for the End of Treatment Visit (EoT) will be performed. The complete End of Treatment eCRF documentation should be done within one week. If ribociclib is permanently discontinued, the patient will be considered to have completed study treatment. All patients must have safety evaluations for 30 days after the last dose of study drug. AEs/SAEs with a suspected causality to study treatment must be reported beyond this 30 day safety interval.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7-1. If they fail to return

for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them.

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.

Table 7-1 Visit evaluation schedule

	Screening/ Baseline Day -21 to C1D1	Cycle 1 Day 1	Cycle 1 Day 15 (+/- 3d)	Cycle 2 Day 1 (+/- 3d)	Cycle 2 Day 15 (+/- 3d)	Cycle 3 Day 1 (+/- 3d)	[redacted]	Cycle 5 Day 1 (+/- 3d)	Cycle 6 Day 1 (+/- 3d)	Cycle 7 Day 1 (+/- 3d)	Further cycles (+/- 3d)	Symptomatic Progress[10]	EOT	Follow up	P&S Follow up
Visit no.	**1**	**2**	**3**	**4**	**5**	**6**		**8**	**9**	**10**	**11-n**	**S**	**N**	**EOT + 30 days**	**PFS-FU**
Demography/ informed consent	X														
Inclusion/ exclusion criteria	X														
Relevant medical history/current medical conditions	X														
Diagnosis and extent of cancer	X														
Prior/post antineoplastic therapy	X													X	(X)[7]
Vital signs, Weight, Physical examination, ECOG status, Height[6]	X	X		X		X		X	X	X	Every cycle until C13, then every 12 weeks	X	X		
Prior/concomitant medications	X	X	X	X	X	X		X	X	X	X	X	X	X	
Pregnancy Test (for premenopausal women)[8]: ***Confirmed negative serum pregnancy test***	X														
pregnancy test,		X		X		X		X	X	X	X	X	X	X	
FSH, estradiol[11]	X	X		X		X		X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X		X	X	X	X	X	X	X	

	Screening/ Baseline Day -21 to C1D1	Cycle 1 Day 1	Cycle 1 Day 15 (+/- 3d)	Cycle 2 Day 1 (+/- 3d)	Cycle 2 Day 15 (+/- 3d)	Cycle 3 Day 1 (+/- 3d)		Cycle 5 Day 1 (+/- 3d)	Cycle 6 Day 1 (+/- 3d)	Cycle 7 Day 1 (+/- 3d)	Further cycles (+/- 3d)	Symptomatic Progress[10]	EOT	Follow up	P&S Follow Up
Hematology, Biochemistry[8] *Please document if clinically indicated/significant*	X (fasting)	(X)*	X	X	X	X		X	X	X	X	X	X		
ECG[9]	X (D-7 to -1) (anytime)		X (anytime)	X (anytime)	X (anytime)	X (anytime)		X (anytime)	X (anytime)	If clinically indicated (anytime)			X (anytime)		
Urinalysis, Serum Lipid Profile, INR[8]	X (fasting)							cally indicated							
Tumor evaluation: *CT for chest, abdomen, pelvis*	X[1]									X	(every 12 weeks)	X	(X)[2,§]		(X)[2,5]
Tumor evaluation: *CT / MRI for Brain if clinically indicated*	(X)[1]									(X)[2]	(every 12 weeks)[2]	(X)[2]	(X)[2,§]		(X)[2,5]
Tumor evaluation: *Bone Scan*	X[3]														
Tumor evaluation: *Bone X-Ray / Bone CT, Skin lesion photography*	(X)[4]									(X)[4]	(every 12 weeks)[4]	(X)[4]	(X)[2,§]		(X)[2,5]
Ribociclib/ letrozole (and goserelin) Dosing		Continu						the trial							
Patient Diary		X		X		X		X	X	X	X	X	X		
EORTC QLQ-C30 & module BR-23		X		X		X		X	X	X	Every cycle until C13, then every 12 weeks	X	X	X	
Progression / survival status[7]															P&S[7] X

Note: 1 Cycle = 28 days

*not necessary if last assessment was within 7 days before first intake of study medication.
§if EOT occurs for other reason than progression and patient withdraws consent for PFS follow up, if last tumor evaluation is older than 12 weeks.
[1]Existing radiologic assessments can be used if assessed up to 28 days prior to C1D1. A corresponding RECIST evaluation should be performed and documented.
[2]If findings at baseline evaluation.
[3]Existing bone scans can be used if assessed up to 56 days prior to C1D1.
[4]Positive areas on bone scans must be assessed by X-ray or CT scan with bone windows on screening/baseline and should continue to be assessed using the same modality. (X-ray or CT scan with bone windows) every 12 weeks. Not all positive areas need to be followed up (non-target lesions) if significant and relevant tumor burden can be assessed by CT.
[5]All patients being discontinued from the study medication for other reasons than tumor progression (or death) should be scheduled for tumor evaluation at 12 week intervals after discontinuation until progression or LPLV occurs, whichever occurs first.
[6]Height is required only at baseline
[7]Survival information can be obtained via phone every 12 weeks, and information will be documented in the source documents and relevant eCRFs.
After the last patient in the trial has taken the last dose of Ribociclib, the post-antineoplastic treatment, current progression and survival status for all patients will be updated finally and recorded in the CRF.
[8]Excisting assessment results can be used if assessed up to 21 days prior to C1D1.
[9]Excisiting ECG assessment can be used if it was within 7 days before first intake of study medication.
PPD

[11] For premenopausal patients; for postmenopausal patients, menopausal status should be confirmed according to local standard

7.1.1 Screening

The screening/baseline visit will occur maximum 21 days prior to first dose of the study drug ribociclib and starts with the signature of the individual ICF.

Patient must provide a signed Informed Consent Form (ICF) prior to any study specific screening evaluations.

The investigator must review inclusion/exclusion criteria and document the patient's eligibility in the patient record.

Re-screening of patients is only allowed once per patient if the patient was not registered as entering the treatment phase before (i.e. first study drug intake). 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.

In case re-screening occurs, all evaluations re-assessed should meet the eligibility criteria.The following data will be collected for all screening failures:

- Informed consent signed
- Inclusion/exclusion (reason for failing)
- Demographics
- SAE data (if applicable).

7.1.1.1 Information to be collected on screening failures

Patients who signed the informed consent and are screened and do not meet all entry criteria will not be entered into the study. Such patients are considered to be screen failures. The reason for not being started will be entered in the site's screening failure log and on screening failure page in CRF.

7.1.1.2 Patient demographics and other baseline characteristics

The following assessments and procedures will be performed within 21 days prior the start of study treatment:

- Obtain patient's written informed consent form.
- General demography including age and gender.
- Medical history/current medical conditions (including prior concomitant medications within the last 4 weeks prior to Day 1).
- History and current disease status (including staging, diagnosis information, previous anti-cancer treatments and sites of disease). The following information must be collected for all previous anticancer therapies: date start, date end, setting (neoadjuvant, adjuvant, metastatic), best response, reason for treatment discontinuation.

Additionally, to determine eligibility at the screening visit, the following assessments will be performed:

- Physical examination, height and weight.
- Vital signs including blood pressure and heart rate.
- Existing ECG assessment can be used if it was within 7 days before first intake of study medication.
- ECOG performance status

- Safety laboratory assessments such as hematology, biochemistry, serum lipid profile, coagulation and urinalysis should be performed locally at the investigator's discretion and are not captured on the CRF. Laboratory assessments performed within 21 days prior to C1D1 may be used. If, at screening, laboratory results are out of range and clinically significant, these results should be captured on the medical history/current medical conditions CRF.
- Radiological tumor assessments at baseline:
  - CT for chest abdomen and pelvis unless performed within 28 days prior to C1D1. CT scan with contrast media should be used except for patients who are allergic/sensitive to the radiographic contrast media. CT for chest and abdomen may be replaced by MRI if clinically contraindicated, e.g. allergy/sensitivity to the radiographic contrast media, metastatic presentation, after prior consultation and approval by Novartis.
  - Brain: CT or MRI if CNS metastases are present unless performed within 28 days prior to C1D1.
  - Whole Body Bone Scan unless performed within 56 days prior to C1D1.

7.1.2 Treatment period

Ribociclib will be dosed starting on treatment Day 1 (Visit 2). Patients will be instructed to take 3 tablets of 200 mg ribociclib orally with a large glass of water, once daily at the same time each day with or without food for 21 days, followed by 7 days without taking ribociclib. Patients will be instructed to inform the investigator of the date of first ribociclib study drug intake.

Letrozole will be dosed starting on treatment Day 1 (Visit 2). Patients will be instructed to take 1 tablet of 2.5 mg letrozole orally with a large glass of water at the same time each day in the morning. Package insert instructions should be followed.

For premenopausal women and men, goserelin will be subcutaneously injected on Day 1 of each cycle. Package insert instructions should be followed.

Patients will continue to be treated per protocol until documentation of disease progression, unacceptable toxicity, death or discontinuation due to any other reason. Treatment beyond progression is at the discretion of the investigator. Information on drug exposure will be collected on the Dosage Administration Record page of the eCRF.

For details of assessments, refer to Table 7-1. The investigator and/or study personnel will assess compliance at each patient visit.

7.1.3 End of treatment visit including study completion and premature withdrawal

At the time patients discontinue study treatment a visit should be scheduled no more than 7 days later, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

Patients who discontinue study treatment for other reasons than progression also should return for tumor assessments every 12 weeks until disease progression and should not be considered withdrawn from the study. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the progression of the disease.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment Disposition CRF page.

If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the Study Phase Completion Disposition CRF (SEC) page.

End of treatment/Premature withdrawal visit is not considered as the end of the study.

7.1.3.1 Study completion

The end of treatment (LPLT=EOT) for all patients is planned80 weeks after the first intake of ribociclib of the last patient (LPFT) or progression of disease of all patients, whichever occurs first. Patients will be followed for safety for 30 days after the individually last dose of study drug to achieve the end of study (LPLV). After last patient last treatment (LPLT), the post-antineoplastic treatment, the current progression and survival status for all patients will be updated finally and recorded in the eCRF.

7.1.3.2 Criteria for premature patient withdrawal

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

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

- Pregnancy
- Subject decision
- Lost to follow up

7.1.4 Follow up period

All patients must be followed for 30 days after the last dose of study drug for safety assessment (AEs and/or SAEs).

All new anticancer therapies given after the last dose of the study drug ribociclib will be recorded on eCRF pages designed to capture antineoplastic therapies within 30 days following discontinuation from the study.

All patients being discontinued from the study medication for other reasons than tumor progression (or death) should be scheduled for tumor evaluation at 12 week intervals after discontinuation until progression or LPLV occurs, whichever occurs first.

Survival status and the current progression will be updated for all patients finally and recorded in the eCRF after last patient last treatment (LPLT) until LPLV. Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator 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.

7.1.5 Survival follow up

All patients will be followed up for survival status every 12 weeks regardless of treatment discontinuation reason until death, lost to follow-up, or withdrawal of consent to survival follow-up. Additional survival assessments may be performed outside the 12 weeks follow up schedules if a survival is required for an interim assessment to meet safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor assessment and response will be evaluated according to RECIST (Version 1.1) (Protocol Post-text Supplement: 1). All radiologic assessments must be performed within a +/- 7 day window of the visit.

Patients should have either at least one lesion that can be measured as per RECIST criteria OR have bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease OR have non-measurable disease.

For patients with measurable disease at screening (as per RECIST criteria), tumor progression will be evaluated every 12 weeks until progression or End of study, whichever is first (according to the RECIST 1.1 criteria). All tumor evaluations performed routinely in addition to the above mentioned will be evaluated and documented according to RECIST 1.1 as well. All patients being discontinued from the study for disease progression must have their progression documented using the criteria specified in RECIST 1.1.

Bone scans must be performed at screening within 56 days before C1D1. Positive areas on bone scans must be assessed by X-ray or CT scan with bone windows, prior to C1D1 and should continue to be assessed using the same modality (X-ray or CT scan) every 12 weeks until progression or End of study. Additional bone scans should be performed if clinically indicated. Abnormalities found on subsequent bone scans must be confirmed by X-ray or CT scan. Bone scans may be replaced by whole body CT, provided that this is local standard. The whole-body CT must be performed within a +/- 7 days window of the visit.

Color photography, including a metric ruler to estimate the size of the lesion, must be acquired for all skin lesions present at baseline. These should be followed throughout the study according to the schedule outlined in Table 7-1.

All patients being discontinued from the study for other reasons than tumor progression (or death) should be scheduled for tumor evaluation at 12 week intervals after discontinuation until LPLV occurs.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline for each study tumor assessment after start of study treatment.

Response will be assessed by local radiology review. The decision regarding patient management will remain with the local investigator, there will be no central review in this study. The same radiologist/physician should perform the evaluation for each individual patient for the entire duration of the study.

A CT scan of the chest, abdomen and pelvis will be performed at screening (≤ 4 weeks prior to the first dose of Ribociclib) and periodically as indicated in Table 7-1. CT Scans with contrast media should be used except for patients who are allergic/sensitive to the radiographic contrast media.

All patients should have at least one lesion that can be accurately measured in at least one dimension ≥ 10 mm with conventional imaging techniques or ≥ 10 mm with spiral CT OR bone lesions such as lytic or mixed (lytic + sclerotic) in the absence of measurable disease OR other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

For patients with measurable disease at baseline, progression will be determined according to the RECIST 1.1 criteria (see Appendix 14.2. for details).

In the absence of measurable disease at baseline, the following will be considered progression among patients with lytic or mixed (lytic + sclerotic) bone lesions:

- The appearance of one or more new lytic lesions in bone
- The appearance of one or more new lesions outside of bone
- Unequivocal progression of existing bone lesions

Note: Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless one of the above-mentioned criteria is fulfilled.

Non measurable disease:

Complete Response (CR) is considered as disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

NCRNPD is considered as persistence of one or more non-target lesion(s).

Progressive Disease (PD) is considered as appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

7.2.1.1 Treatment beyond progression

Upon radiologic progression according to RECIST 1.1 treatment with study drug may be continued at the discretion of the investigator until a clinically symptomatic progression occurs. Symptomatic progression will be assessed every 12 weeks until progression or End of study. Clinically symptomatic progress is judged by the investigator and must be documented accordingly in the source documentation and eCRF. A radiologic assessment must be performed upon symptomatic progression.

7.2.2 Safety and tolerability assessments

Safety will be monitored by collecting and assessing all adverse events, including serious adverse events, the regular monitoring of hematology, blood chemistry, vital signs, physical

condition and ECG. These assessments should be performed ± 3 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study, starting after the patient has provided informed consent (Refer to Table 7-1).

Toxicity will be assessed using the NCI-CTCAE Common Terminology Criteria for Adverse Events, version 4.03 (CTCAEv4.03). For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

Physical examination should include a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes and extremities).

Physical examination will be performed at screening, on treatment Day 1 (prior to administration of the study drug, unless physical examination in screening was done less than 7 days before Day 1), on Day 1 of cycle 1-13, every 12 weeks thereafter, and at the End of treatment.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that were present prior to the signing of the informed consent must be documented on the Medical History / Current Medical Conditions eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF.

Heigth will be measured at screening only.

Weight will be measured at screening and when clinically indicated.

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

7.2.2.2 Vital signs

Vital signs will be recorded on the appropriate eCRF pages. Vital Signs should be recorded at screening, on Day 1 of cycle 1-13, every 12 weeks thereafter, and at the End of treatment. Heart rate, temperature and blood pressure will be measured according to normal medical practice.

The particular clinical findings that were present prior to the signing of the informed consent must be documented in the Relevant Medical History eCRF. The findings that begin or worsen after informed consent must be documented in the Adverse Event eCRF.

7.2.2.3 Performance status

The performance status will be scored using the ECOG Performance Status Scale.

ECOG Performance Status will be assessed and recorded at screening, on Day 1 of cycle 1-13, every 12 weeks thereafter, and at the End of treatment..

Assessment of ECOG Performance Status will be performed on the scheduled day, even if study medication is being held. The ECOG Performance Status Scale Index (Oken, 1982) allows patients to be classified as to their functional impairment; the definition of scores in relation to the Performance Status is given in Table 7-2.

Table 7-2 ECOG Performance Status Scale

Score	Performance 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 housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

7.2.2.4 Laboratory evaluations

Laboratory evaluations should be performed locally at every protocol required visit (Table 7-1) or as frequently as clinically indicated.

The frequency of the assessments is indicated in *Table 7-1*. All scheduled laboratory evaluations must be obtained ≤ 7 days of the specified time periods, whether or not study treatment is administered. Screening examinations performed ≤ 7 days of the first dose of study treatment do not need to be repeated on Day 1.

Laboratory values will not be documented in the eCRF unless clinically significant.

Any particular clinically significant findings present at screening at the time of informed consent must be documented in the Relevant Medical History/Current Medical Conditions eCRF. Abnormal laboratory parameters that induce clinical signs or symptoms, require therapy (e.g. hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug(s) constitute an adverse event (Section 8.1.2), must be recorded on the Adverse Event eCRF.

Laboratory certificates will be collected for this study.

Table 7-3 Local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), hemoglobin (Hgb) and platelet count.
Biochemistry with fasting glucose	Sodium, potassium, calcium, corrected calcium, magnesium, total protein and albumin. AST (SGOT), ALT (SGPT), total bilirubin, direct bilirubin, GGT and alkaline phosphatase,and LDH. At Baseline and if clinically indicated: urea, creatinine, fasting glucose
Coagulation	At Baseline and if clinically indicated: INR
Fasting Lipid Panel	At Baseline and if clinically indicated: Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides

7.2.2.4.1 Hematology

Hematology tests are to be performed according to the Visit Schedules outlined in Table 7-1. For details of the Hematology panel refer to Table 7-3 Hematological tests will be performed at screening, on treatment Day 1 (repeated prior to administration of the study drug, if greater than 7 days prior to Day 1), Cycle 1 Day 15, Cycle 2 Day 1 and 15 and Day 1 of each subsequent cycle and at End of treatment.

In the event of Grade 2, Grade 3 or Grade 4 hematological toxicities that require study drug dose modifications or interruptions, hematological tests should be repeated weekly until recovery to the baseline value or Grade 1.

7.2.2.4.2 Clinical chemistry

Serum chemistry tests are to be performed according to the Visit Schedules outlined in Table 7-1. For details of the biochemistry panel refer to Table 7-3.

Serum chemistry should be performed at screening, on treatment Day 1 (repeated prior to administration of the study drug, if greater than 7 days prior to Day 1), Cycle 1 Day 15, Cycle 2 Day 1 and Day 15 and Day 1 of each subsequent cycle and at End of treatment.

In the event of Grade 2, Grade 3 or Grade 4 non-hematological toxicities that require study drug dose modifications or interruptions, biochemistry tests should be repeated weekly until recovery to the baseline value or Grade 1.

Note: In the phase III study MonaLEEsa-2 the majority (83.8%; 31/37) of the grade 3/4 ALT and AST increases with the combination therapy occurred during the first 6 months of treatment. The median time-to-onset of grade≥ 3 ALT/AST elevation was 57 days and 62 days, respectively (based upon medians of patients with events). The median time to resolution (to normalization or grade <3) (again based upon medians of patients with events) was 24 days in the ribociclib plus letrozole treatment group vs. 19 days for the placebo plus letrozole group.
In this study, laboratory values will be performed at the beginning of each cycle to assure that LFT abnormalities will be appropriately captured with this monitoring schedule.

7.2.2.4.3 Serum lipid profile

Serum lipid tests are to be performed according to the Visit Schedules outlined in Table 7-1. For details of the lipid panel refer to Table 7-3.

A serum lipid profile assessment according to local standard should be performed at screening and as clinically indicated.

In the event of Grade 2, Grade 3 or Grade 4 toxicities serum lipid tests should be repeated weekly until recovery to the baseline value or Grade 1.

7.2.2.4.4 Urinalysis

Urinalysis is to be performed at Screening/Baseline according to local standard and as clinically indicated (dipstick analysis is sufficient).

7.2.2.4.5 Pregnancy and assessments of fertility

For pre- or perimenopausal patients, a serum or urine pregnancy tests (patients who have undergone a hysterectomy do not need pregnancy tests performed) are to be performed according to the Visit Schedules outlined in Table 7-1. At screening, a serum pregnancy test should be performed for pre- and perimenopausal patients, regardless of the age of the patients, while at baseline, during the study, and at the end of trial, urinary pregnancy tests are sufficient. Simultaneously, FSH and/or estradiol should be measured to ensure postmenopausal status.

7.2.2.5 Cardiac assessments

7.2.2.5.1 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed after the patient has been resting for 5-10 min prior to each time point indicated in Table 7-4 below. Tracings must be dated and signed by the investigator (or his/her designee) and filed with the patient's source documentation. QTc intervals should be calculated according to Fridericia. Each ECG tracing should be labeled with the study number, patient number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening when the patient signed informed consent should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated; any clinically relevant findings should be added to the Adverse Events eCRF.

Table 7-4 ECG collection plan

Cycle	Patients	Day	Time
Screening	All	-7 to -1	Anytime
1	All	Day 15	Anytime
2	All	Day 1	Anytime
	All	Day 15	Anytime
3-6	All	Day 1	Anytime
All other cycles	Patients with QTcF ≥ 481 ms at any time prior to cycle 7	Day 1	Anytime
EOT			Anytime
Unscheduled ECG			Anytime

If any of the readings include an abnormal ECG or an average QTcF value of ≥ 481 ms is obtained at any time after enrollment in the study, treatment must be interrupted, repeat ECG and follow management guidelines detailed in Table 6-5.

7.2.3 Biomarkers

This clinical study includes mandatory biomarker components that are supported by an exploratory objective. [redacted]

Table 7-5 Biomarker sample collection plan

Sample Type	*Volume*	*Visit*	*Time point*
Tumor samples			
tumor block of the primary tumor and the re-biopsy upon metastatic progression/ recurrence, if available	N/A	Screening	Day -21 to Day 1
Blood samples			
Blood for biomarker analysis (mandatory)	60 mL	Cycle 1 Day 1	Pre-dose
	60 mL	Cycle 1 Day 15	Anytime
	60 mL	Cycle 4 Day 1	Pre-dose
	60 mL	End of treatment	Anytime

[redacted]

Tumor tissue

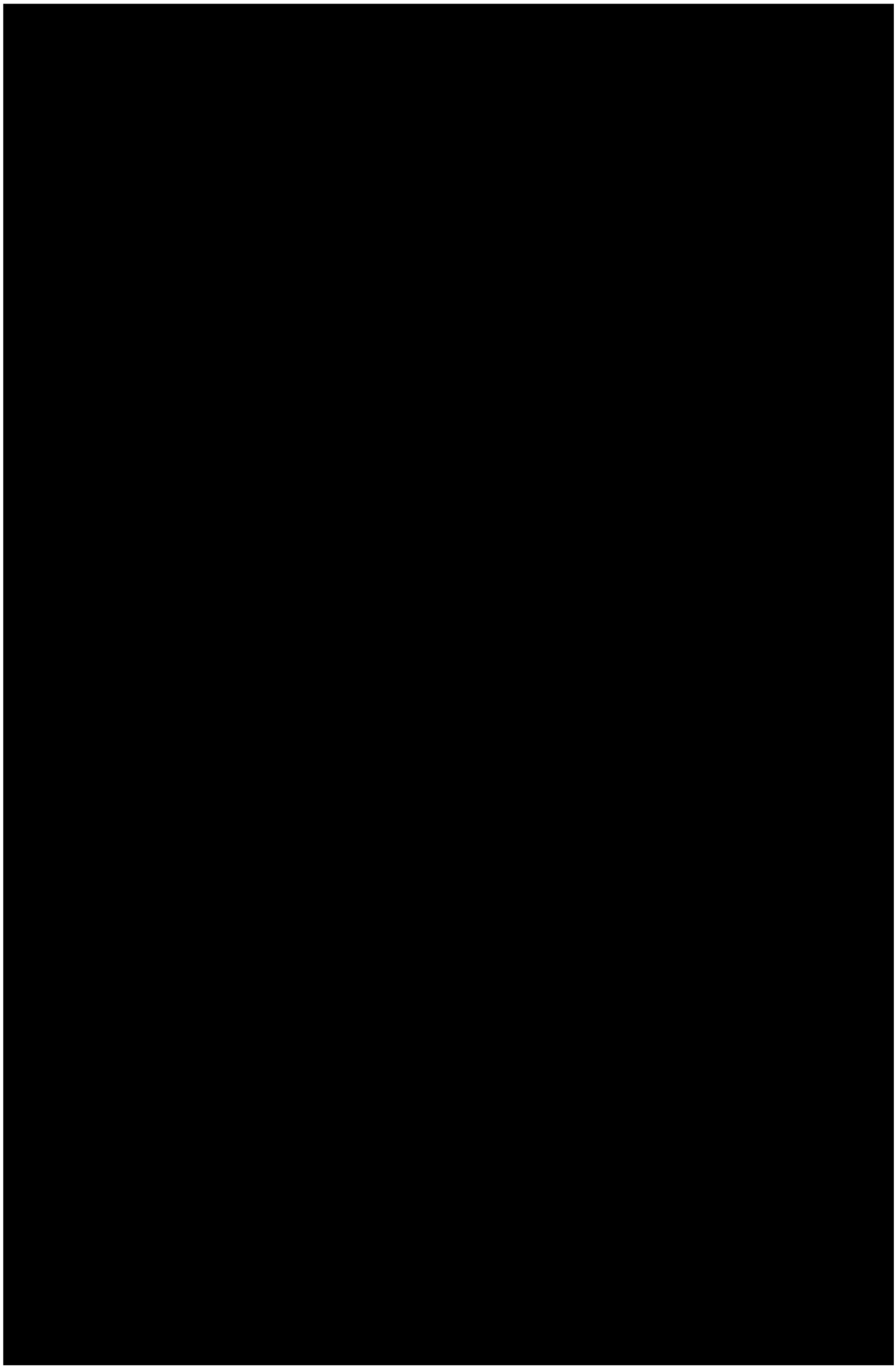
Tumor tissue samples will be collected in this trial for identifying biomarkers [redacted]. It is highly recommended that an archival FFPE block of the initial tumor and of a metastatic lesion (if available, preferred) is provided. Receipt of tumor tissue will not delay enrollment. All specimens will be sent to a Novartis designated laboratory for analysis. Further details on preparation of the tumor biopsies and biomarker analysis will be provided in the Laboratory Manual. [redacted]

Pharmacogenetics

Pharmacogenetics is able to provide genetic markers that could predict the prognosis of breast cancer patients (Azzato et al., 2010; Fagerholm et al., 2008; Schroth et al., 2009), but also the toxicity of treatments such as aromatase inhibitor therapy (Ingle et al., 2010). Furthermore, there is evidence that - within an individual - a tumor will exhibit distinct molecular patterns based on its germline genetic makeup. (Garcia-Closas et al., 2008; Reeves at al., 2010)

The direct involvement of genetic markers in the metabolism and the pharmacokinetics of a drug, the influence of the inherited genetic trait on the molecular profile of the tumor and the acquired tumor mutations could have an influence on an individual's prognosis.

[redacted]



[redacted]

Details regarding addresses of shipments, carrier recommendations, labeling of the parcels, days of shipments, contact details and other samples logistics will be provided in a separated laboratory manual.

[redacted]

7.2.3.1.2 Other assessments

No additional tests will be performed on patients entered into this study.

7.2.4 Patient reported outcomes

The following questionnaires will be used to assess the health related quality of life: EORTC QLQ-C30 and the breast module BR23.

All questionnaires will be completed on Day 1 at every cycle until C13 and every 12 weeks thereafter until safety follow up.

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

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

Upon radiologic progression according to RECIST 1.1 treatment with study drug may be continued at the discretion of the investigator until a clinically symptomatic progress occurs. In this case, the quality of life questionnaires must be completed according to Visit schedule. If radiologic progression occurs, before Cycle 13 monthly and after Cycle 13 every 12 weeks until symptomatic progression or End of study as well as upon symptomatic progression.

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, 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 CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. 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 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study If death is not caused by progression of the disease, it has to be reported as SAE on the SAE report form. Adverse events with death as outcome must be documented as SAE on the SAE report 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:

- The severity grade (CTCAE Grade 1-4).
- Its duration (Start and end dates).
- Its relationship to the study drug (Yes or No).

- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
- Whether diagnostics, medication with which dosages or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy).
- Setting: in or outpatient treatment.
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown).
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.

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 CRF.

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), , 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 CRF. 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 (severe) or 4 (life-threatening) event 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**: Hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- **Note**: 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.

Protocol exempt SAEs

SAEs specifically defined in the protocol and where there has been a clear agreement with regulators not to collect these SAEs in the safety database, provided the information is collected elsewhere. In this existing protocol, progression of malignancy (including progression of malignancy with fatal outcome).

8.2.2 Reporting

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

Any SAEs experienced after this 30-day period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment (ribociclib, letrozole and/or goserelin).

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

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 send the completed, signed form by fax within 24 hours to the oncology Novartis Patient Safety department.

The telephone and telefax number of the contact persons in the local department of Novartis Patient Safety, specific to the site, are listed in the investigator folder provided to each site.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original 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, and whether the patient continued or withdrew from study participation.

An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Patient Safety 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 Pregnancies

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 Patient Safety. 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.

8.4 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 Brochure. 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.

8.5 Steering Committee

A Study Steering Committee (SSC) will be constituted to oversee the conduct of the study and making any necessary recommendations as needed. 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.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects 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 subjects 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 subjects 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 CRFs 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 CRFs, 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 CRFs 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 CRF 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 CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

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.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

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.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Trial Statistician and the Therapeutic Area Head.

10 Statistical methods and data analysis

The study is designed as an open-label, single-arm, phase IIIB trial to assess the efficacy and safety of ribociclib plus letrozole in women with hormone receptor positive advanced breast cancer.

The data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations. The primary efficacy and safety analysis will be conducted on all patient data at the time all patients who are still receiving study drug will have completed at least 24 weeks of treatment (or discontinued prematurely). The additional data for any patients continuing to receive study drug past these

times, as allowed by the protocol, will be further summarized in a report once these patients complete the study.

In general, categorical variables will be summarized by absolute and relative frequencies. Continuous variables will be summarized by descriptive statistics (number of valid and missing observations, mean, standard deviation, minimum, median and maximum). Time-to-event data including rates of affected patients will be assessed using the Kaplan-Meier method. The primary aim of this trial is in estimation rather than significance testing of statistical hypotheses. Thus, mainly statistical estimators along with appropriate two-sided 95% confidence intervals will be used. However, changes from baseline may be explored using suitable statistical tests for paired samples. No adjustment for multiplicity is foreseen due to the exploratory nature of the trial.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned. Patients will be analyzed according to the treatment they have been assigned to.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment (regimen) they actually received.

A precise definition of "actually received" will be added in the RAP.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the CSP. The PPS may be analysed in case a substantial number of patients was not compliant with requirements of the CSP.

Oncology standards for protocol deviations **potentially** leading to exclusion from the PPS are

- type of indication different from those required by the CSP (e.g., incorrect histology/cytology, not refractory, not metastatic, different grade of cancer, etc.)
- if prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens
- missing or incomplete documentation of stage of disease (as required in the CSP)
- if ECOG performance status at least 1 category worse than protocol-defined inclusion criteria
- another anti-neoplastic therapy administered after start of study treatment and prior to first tumor assessment

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics will be summarized for the Full Analysis Set (FAS). Baseline characteristics include prior medication, past/current medical conditions and disease history. Categorical variables will be summarized by absolute and relative frequencies. Continuous variables will be summarized by descriptive statistics (number of valid and missing observations, mean, standard deviation, minimum, median

and maximum, 25th and 75th percentiles). Time-to-event data including rates of affected patients will be assessed using the Kaplan-Meier method.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Duration (days) of drug exposure will be summarized using descriptive statistics separately for ribociclib, letrozole (or goserelin), respectively. Duration of drug exposure will be calculated as the difference between the last and first day of drug application +1. Dosage averages will be calculated including and excluding zero doses for periods of temporary interruption of treatment regardless of whether this was due to safety reasons or patients' non-compliance. Average daily dose levels will be summarized descriptively. Frequencies of the number of patients with any dose reduction (including temporary dose interruption) as well as the number of dose reductions by reason will be given. These analyses will be performed for the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be coded according to the WHO Drug Reference List and summarized by ATC class and preferred term using frequency distributions.

10.4 Primary objective

The primary objective of this study is the assessment of the clinical benefit rate for the total population and for cohorts A and B separately:

- To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole among postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no prior treatment for advanced disease(Cohort A).
- To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole and goserelin among pre-, and perimenopausal women who received no prior treatment for advanced disease as well as pre-, peri- and postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no more than 1 prior chemotherapy and 2 prior lines of endocrine therapy for advanced disease (Cohort B).

10.4.1 Variable

The **Clinical Benefit Rate (CBR)** is the proportion of patients with a best overall response of confirmed complete (CR) or partial (PR) response or stable disease (SD) or non-complete response, non-progressive disease (NCRNPD) by Week 24. The best overall response for each patient is determined from the sequence of investigator overall lesion responses according to RECIST 1.1. To be assigned a best overall response of CR at least two determinations of CR at least 4 weeks apart before progression are required. To be assigned a best overall response of PR at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) are required. To be assigned a stable disease, two determinations of SD at least 12 weeks apart (and not qualifying for PR or PD) are required.

For further details, please refer to Appendix 14-2: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1).

10.4.2 Statistical hypothesis, model, and method of analysis

In this single-arm trial, the primary objective is to estimate the CBR. Therefore, no statistical hypothesis or model is underlying the analysis.

The CBR (best overall response of CR or PR or SD or NCRNPD) as well as individual response categories (CR, PR, SD, PD, NCRNPD or unknown) will be summarized using frequency tables together with their associated two-sided exact 95% confidence intervals (Clopper-Pearson method). The Full Analysis Set will be used for the primary efficacy analysis.

10.4.3 Handling of missing values/censoring/discontinuations

Since the definition of the primary variable is derived from tumor assessments based on RECIST 1.1 criteria, these criteria apply for the handling of missing values in tumor assessments. 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 (see Post-text supplement 1). If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen. Patients with a best overall response assessment of unknown (UNK) will not be regarded as 'responders' but will be included in the denominator for the calculation of the ORR for the FAS.

10.4.4 Supportive analyses

CBR by Week 24 will be additionally presented for the Per-protocol Set. Furthermore, the CBR may be summarized by subgroups for the FAS and PP set, respectively.

10.5 Secondary objectives

10.5.1 Efficacy (secondary)

The following secondary efficacy variables will be analyzed in an explorative manner for the full analysis set (FAS): CBR subgroups, ORR by Week 24, Progression-free survival (PFS) and overall survival (OS).

CBR Subgroups

- To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole and goserelin among pre- and perimenopausal women who received no prior treatment for advanced disease.
- To assess the clinical benefit rate (CBR) after 24 weeks for ribociclib (LEE011) in combination with letrozole (and goserelin) among pre-, peri- and postmenopausal women and men who received prior treatment for advanced disease.

ORR by Week 24

The ORR by Week 24 will be derived from the sequence of overall lesion responses as described for the primary efficacy variable. The ORR by Week 24 will be summarized using frequency tables presenting absolute and relative frequencies together with appropriate confidence intervals.

Progression-free survival

Progression-free survival (PFS) is the time from date of 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. Disease progression for primary efficacy endpoint derivation will be assessed using the local (treating center's radiologist's) investigator's tumor assessment. PFS will be summarized using the Kaplan-Meier method. Percentiles (25%, median, 75%) of the event time distribution will be presented along with their two-sided 95% confidence interval. Additionally, Kaplan-Meier estimates for the proportions of patients progression-free by Week 48 and Week 72 will be presented. The Kaplan-Meier curve will be displayed graphically.

Overall survival

Overall survival (OS) is defined as the time from date of 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 contact. OS will be summarized using the Kaplan-Meier method as described above. The Kaplan-Meier curve will be displayed graphically. Additionally, the proportion of patients alive at 48 and 96 weeks will be presented

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. vital signs, and special tests) will be considered as appropriate. For all safety analyses, the safety set will be used.

All listings and tables will be presented by pretreatment group (postmenopausal patients without prior treatment for advanced disease, pre- and perimenopausal patients without prior treatment for advanced disease and pre-, peri and postmenopausal patients with prior treatment for advanced disease).

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to *30* days after last dose of study medication
3. post-treatment period: starting at day *30*+1 after last dose of study medication.

10.5.2.2 Adverse events (AEs)

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

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

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Data collected by AE CRFs will be coded using the MedDRA dictionary. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by MedDRA system organ class and preferred term using frequency distributions. Additionally, AE will be summarized by maximum severity (based on CTCAE grades), and for AE with suspected drug relation, serious AE (SAE), and AE leading to permanent discontinuation of study drug. All information pertaining to AE noted during the study will be listed by patient, detailing the verbatim term given by the investigator, MedDRA preferred term and system organ class, start/end dates, severity, seriousness, relationship to study drug and action taken. The AE onset will also be shown relative (in number of days) to the date of initial dose.

10.5.2.3 Laboratory abnormalities

Normal laboratory values will not be documented in the CRF. Abnormal laboratory parameters that induce clinical signs or symptoms, require therapy (e.g. hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug(s) constitute an adverse event (Section 8.1.2), must be recorded on the Adverse Events CRF and are coded and summarized accordingly as described in 10.5.2.2.

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

10.5.2.4 Other safety data

Data from other tests (e.g., electrocardiogram or vital signs) will be summarized descriptively as appropriate. Notable values will be flagged, and any other information collected will be listed as appropriate.

ECG

ECG results will be reported only if the criteria for SAE are met.

Vital signs

Definitions of notably abnormal results have to part of the CDP, MAP, CSP and RAP.

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

ECOG Performance Status

The ECOG Performance Status will be summarized using frequency distributions by visit. Shifts from baseline value to worst post-baseline value will be summarized using frequency distributions.

10.5.3 Biomarkers

Since this clinical trial was not designed to address specific biomarkers-related hypotheses, the analysis of this data should be viewed as exploratory and hypotheses generating.

[redacted]

10.5.3.1 Outline of the data analysis

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the analysis plan or in a stand-alone analysis plan document, as appropriate.

10.5.3.2 Data handling principles

Immunohistochemistry (IHC) data reported from the lab will include quantitative data such as percent tumor and percent positive cells or a semi quantitative measure of protein expression in cellular compartments (i.e. cytoplasm, nucleus, membrane). The pathologist determines whether the staining in a cellular compartment is absent (0+), slight (1+), moderate (2+), or strong (3+).

10.5.3.3 Data analysis principles

10.5.3.3.1 Analysis sets

The standard analysis sets will be used according to the purpose of a given analysis (e.g. FAS to describe biomarkers, safety/per-protocol set to assess the relationship between biomarkers and selected safety/efficacy endpoints). The number of patients included in a

given analysis will reflect the number of patients in the chosen analysis set which have a valid biomarker assessment.

10.5.3.3.2 Analysis methods

Tumor tissue samples and blood samples will be collected in this trial [redacted]

10.5.4 Patient-reported outcomes

Health-related quality of life (HRQoL) will be assessed using the EORTC QLQ-C30 and BR23 questionnaires. Scoring will follow the instructions of the respective manuals.

Descriptive statistics will be used to summarize the individual item and scored sub-scale scores of QoL data at each scheduled assessment time point. Patients will be included if they completed at least one questionnaire item. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period will be included in the change from baseline analyses (assessments after disease progression will be excluded).

10.6 Exploratory objectives

[redacted]

10.7 Interim analysis

Three interim analyses are planned during the study. The first interim analysis will be conducted one year after the first patient has been enrolled and include a preliminary analysis on safety. The second interim analysis will be conducted 12 months after LPFV in the 30% pretreated and premenopausal cohort and will include a preliminary analysis on safety, efficacy and quality of life. The third interim analysis will take place 6 months after the last patient has been recruited and will include a preliminary analysis on safety and efficacy.

10.8 Sample size calculation

Sample size assumptions in this study for postmenopausal patients without prior treatment for advanced disease are based on the data from the CLEE011X2107 study (Juric, poster presented at ASCO 2016), which enrolled a similar patient population.

Regarding patients in later than first lines and pretreated premenopausal patients, assumptions are based on Cristofanilli et al 2016 - PALOMA-3 final analysis.

It is expected that the CBR (based on local assessment) by week 24 is in a range as reported for the CLEE011X2107study for the ribociclib + letrozole group (CBR = 79%, 95% confidence interval [59% to 92%]).
Using the lower limit of the CI (59%) as a pessimistic estimate for the CBR by week 24, a sample size of 500 produces a two-sided 95% confidence interval with a width equal to 8.6 percentage points (the associated 95% CI is [54.7% to 63.3%]). When using the same CBR as observed (CBR 79%), a sample size of 500 produces a two-sided 95% confidence interval with a width equal to 7.2 percentage points (the 95% CI is [75.4% to 82.6%]). Using the upper limit of the CI (92%) as an optimistic estimate for the CBR, a sample size of 500 produces a two-sided 95% confidence interval with a width equal to 4.8 percentage points (the 95% CI is 89.6% to 94.4%]). Assuming an estimated rate of 70% to be recruited in the subgroup of postmenopausal first line patients resulting in a sample size of 350 patients, the width of the confidence interval will be between 10.4 percentage points (pessimistic scenario) and 5.6 percentage points (optimistic scenario).

Regarding the subgroup of second or further treatment lines and premenopausal patients, assuming an estimated rate of 30% to be recruited, and further based on the data as presented by Cristofanili et al. (CBR 67%, 95% CI [61.3% to 71.5%]), the resulting precision based on 150 patients leads to a width of the resulting 95% confidence interval between 15.6 percentage points (pessimistic scenario) and 14.4 percentage points (optimistic scenario).
Thus, a sample size of 500 patients allows estimating the CBR in this patient population with reasonable precision.

10.9 Power for analysis of key secondary variables

Not applicable. Power for analysis of secondary variables was not investigated.

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.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). 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 CRFs.

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.

Additional consent form

Sub-studies and studies with an optional Exploratory Biomarker component will have a separate consent form covering those studies. This informed consent form will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a subject opts not to participate in the optional assessments, this in no way affects the subject's ability to participate in the main research study.

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 assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

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 subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' 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 pseudonimity 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.

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 but not later than 10 working days.

13 References (available upon request)

Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, Kirkland JL, van Deursen JM. (2011) Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature. 2011 Nov 2;479(7372):232-6. doi: 10.1038/nature10600.

Bartkova J, Lukas J, Müller H, Lützhøft D, Strauss M, Bartek J. (1994). Cyclin D1 protein expression and function in human breast cancer. Int J Cancer. 1994 May 1;57(3):353-61.

Beroukhim R, Mermel CH, Porter D, et al (2010) The landscape of somatic copy-number alteration across human cancers. Nature. 463(7283):899-905.

Berry DA, Cirrincione C, Henderson IC, Citron ML, Budman DR, Goldstein LJ, Martino S, Perez EA, Muss HB, Norton L, Hudis C, Winer EP. (2006) Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA. 2006 Apr 12;295(14):1658-67.

Beslija S, Bonneterre J, Burstein HJ, Cocquyt V, Gnant M, Heinemann V, Jassem J, Köstler WJ, Krainer M, Menard S, Petit T, Petruzelka L, Possinger K, Schmid P, Stadtmauer E, Stockler M, Van Belle S, Vogel C, Wilcken N, Wiltschke C, Zielinski CC, Zwierzina H; Central European Cooperative Oncology Group (CECOG). (2009). Third consensus on medical treatment of metastatic breast cancer. Ann Oncol. 2009 Nov;20(11):1771-85. doi: 10.1093/annonc/mdp261. Epub 2009 Jul 16.

Borg A, Zhang QX, Alm P, et al (1992) The retinoblastoma gene in breast cancer: allele loss is not correlated with loss of gene protein expression. Cancer Res; 52: 2991-4

Bosco EE, Wang Y, Xu H, Zilfou JT, Knudsen KE, Aronow BJ, Lowe SW, Knudsen ES (2007). The retinoblastoma tumor suppressor modifies the therapeutic response of breast cancer. J Clin Invest. 2007 Jan;117(1):218-28. Epub 2006 Dec 7.

Buckley MF, Sweeney KJ, Hamilton JA, Sini RL, Manning DL, Nicholson RI, deFazio A, Watts CK, Musgrove EA, Sutherland RL (1993). Expression and amplification of cyclin genes in human breast cancer. Oncogene. 1993 Aug;8(8):2127-33.

Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E; ESMO Guidelines Working Group (2012). Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct;23 Suppl 7:vii11-9.

Chano T, Kontani K, Teramoto K, et al (2002) Truncating mutations of RB1CC1 in human breast cancer. Nat Genet; 31: 285-8

Dickson C, Fantl V, Gillett C, Brookes S, Bartek J, Smith R, Fisher C, Barnes D, Peters G. (1995). Amplification of chromosome band 11q13 and a role for cyclin D1 in human breast cancer. Cancer Lett. 1995 Mar 23;90(1):43-50.

Ellis MJ, Coop A, Singh B, Mauriac L, Llombert-Cussac A, Jänicke F, Miller WR, Evans DB, Dugan M, Brady C, Quebe-Fehling E, Borgs M. (2001). Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol. 2001 Sep 15;19(18):3808-16.

Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, Ginther C, Atefi M, Chen I, Fowst C, Los G, Slamon DJ. (2009). PD 0332991, a selective cyclin D kinase 4/6 inhibitor,

preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res. 2009;11(5):R77. doi: 10.1186/bcr2419.

Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, Ettl J, Patel R, Pinter T, Schmidt M, Shparyk Y, Thummala AR, Voytko NL, Fowst C, Huang X, Kim ST, Randolph S, Slamon DJ. (2014). The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25-35. doi: 10.1016/S1470-2045(14)71159-3. Epub 2014 Dec 16.

Gianni L, Baselga J, Eiermann W, Guillem Porta V, Semiglazov V, Lluch A, Zambetti M, Sabadell D, Raab G, Llombart Cussac A, Bozhok A, Martinez-Agulló A, Greco M, Byakhov M, Lopez Lopez JJ, Mansutti M, Valagussa P, Bonadonna G; European Cooperative Trial in Operable Breast Cancer Study Group. (2005) Feasibility and tolerability of sequential doxorubicin/paclitaxel followed by cyclophosphamide, methotrexate, and fluorouracil and its effects on tumor response as preoperative therapy. Clin Cancer Res. 2005 Dec 15;11(24 Pt 1):8715-21.

Gillett C, Fantl V, Smith R, Fisher C, Bartek J, Dickson C, Barnes D, Peters G. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining. Cancer Res. 1994 Apr 1;54(7):1812-7.

Gillett C, Smith P, Gregory W, Richards M, Millis R, Peters G, Barnes D. Cyclin D1 and prognosis in human breast cancer. Int J Cancer. 1996 Apr 22;69(2):92-9.

Jeffrey R. Infante A phase I study of the single-agent CDK4/6 inhibitor LEE011 in pts with advanced solid tumors and lymphomas. ASCO 2014; abstract 2528

Jeong S, Woo MM, Flockhart DA, Desta Z; Inhibition of drug metabolizing cytochrome P450s by the aromatase inhibitor drug letrozole and its major oxidative metabolite 4,4'-methanol-bisbenzonitrile in vitro. Cancer Chemother Pharmacol. 2009 Oct;64(5):867-75. doi: 10.1007/s00280-009-0935-7. Epub 2009 Feb 7.

Juric et al. Ribociclib (LEE011) and letrozole in estrogen receptor-positive (ER+), HER2-negative (HER2–) advanced breast cancer (aBC): Phase Ib safety, preliminary efficacy and molecular analysis. J Clin Oncol 34, 2016 (suppl; abstr 568)

Lange CA, Yee D.; Killing the second messenger: targeting loss of cell cycle control in endocrine-resistant breast cancer. Endocr Relat Cancer. 2011 Jul 4;18(4):C19-24. doi: 10.1530/ERC-11-0112

Lipton A, Demers LM, Harvey HA, Kambic KB, Grossberg H, Brady C, Adlercruetz H, Trunet PF, Santen RJ.; Letrozole (CGS 20267). A phase I study of a new potent oral aromatase inhibitor of breast cancer. Cancer. 1995 Apr 15;75(8):2132-8.

Lundgren K, Brown M, Pineda S, Cuzick J, Salter J, Zabaglo L, Howell A, Dowsett M, Landberg G; TransATAC investigators. Effects of cyclin D1 gene amplification and protein expression on time to recurrence in postmenopausal breast cancer patients treated with anastrozole or tamoxifen: a TransATAC study. Breast Cancer Res. 2012 Apr 4;14(2):R57.

McIntosh GG, Anderson JJ, Milton I, Steward M, Parr AH, Thomas MD, Henry JA, Angus B, Lennard TW, Horne CH.; Determination of the prognostic value of cyclin D1 overexpression in breast cancer. Oncogene. 1995 Sep 7;11(5):885-91.

Miller TW, Balko JM, Arteaga CL.: Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. J Clin Oncol. 2011 Nov 20;29(33):4452-61. doi: 10.1200/JCO.2010.34.4879. Epub 2011 Oct 17.

Miller TW, Balko JM, Fox EM, Ghazoui Z, Dunbier A, Anderson H, Dowsett M, Jiang A, Smith RA, Maira SM, Manning HC, González-Angulo AM, Mills GB, Higham C, Chanthaphaychith S, Kuba MG, Miller WR, Shyr Y, Arteaga CL. ERα-dependent E2F transcription can mediate resistance to estrogen deprivation in human breast cancer. Cancer Discov. 2011 Sep;1(4):338-51. doi: 10.1158/2159-8290.CD-11-0101. Epub 2011 Jul 20.

Mouridsen H1, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleeboom HP, Jänicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Lassus M, Verbeek JA, Staffler B, Chaudri-Ross HA, Dugan M.; Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol. 2001 May 15;19(10):2596-606.

Murphree AL, Benedict WF (1984) Retinoblastoma: clues to human oncogenesis. Science; 223: 1028-33

Musgrove EA, Caldon CE, Barraclough J, et al (2011) Cyclin D as a therapeutic target in cancer. Nat Rev Cancer 11:558-72.

Theriault RL, Carlson RW, Allred C, Anderson BO, Burstein HJ, Edge SB, Farrar WB, Forero A, Giordano SH, Goldstein LJ, Gradishar WJ, Hayes DF, Hudis CA, Isakoff SJ, Ljung BM, Mankoff DA, Marcom PK, Mayer IA, McCormick B, Pierce LJ, Reed EC, Schwartzberg LS, Smith ML, Soliman H, Somlo G, Ward JH, Wolff AC, Zellars R, Shead DA, Kumar R; National Comprehensive Cancer Network.: Breast cancer, version 3.2013: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2013 Jul;11(7):753-60; quiz 761.

Oesterreich S, Fuqua SAW (1999) Tumor suppressor genes in breast cancer. Endocr Relat Cancer; 6: 405-19

Oken MM, Creech RH, Tormey DC et al. (1982) Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol; 5:649-655.

Olson JA Jr, Budd GT, Carey LA, Harris LA, Esserman LJ, Fleming GF, Marcom PK, Leight GS Jr, Giuntoli T, Commean P, Bae K, Luo J, Ellis MJ.: Improved surgical outcomes for breast cancer patients receiving neoadjuvant aromatase inhibitor therapy: results from a multicenter phase II trial. J Am Coll Surg. 2009 May;208(5):906-14;

Pietilainen T, Lipponen P, Aaltomaa S, et al (1995) Expression of retinoblastoma gene protein (Rb) in breast cancer as related to established prognostic factors and survival. Eur J Cancer; 31A: 329-33

Semiglazov VF, Semiglazov VV, Dashyan GA, Ziltsova EK, Ivanov VG, Bozhok AA, Melnikova OA, Paltuev RM, Kletzel A, Berstein LM.: Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer. 2007 Jul 15;110(2):244-54.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006; 24:3187–3205. doi:10.1200/JCO.2006.06.4451

Trunet PF, Bhatnagar AS, Chaudri HA, Hornberger U.; Letrozole (CGS 20267), a new oral aromatase inhibitor for the treatment of advanced breast cancer in postmenopausal patients. Acta Oncol. 1996;35 Suppl 5:15-8.

Turner NC, et al (2015) Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med; 373(3): 209-219

The Cancer Genome Atlas Network: Comprehensive molecular portraits of human breast tumours Nature 2012 Oct. 04;490:61–70;DOI:doi:10.1038/nature11412

Yu Q, Sicinska E, Geng Y, Ahnström M, Zagozdzon A, Kong Y, Gardner H, Kiyokawa H, Harris LN, Stål O, Sicinski P.: Requirement for CDK4 kinase function in breast cancer. Cancer Cell. 2006 Jan;9(1):23-32.

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 on Oncology Clinical Pharmacology guidance, Drug-Drug Interaction and Co-Medication Considerations (v07, release date: Jan 2018), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http://www.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (www.qtdrugs.org/). Please contact the medical monitor with any questions.

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, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Avasimibe[2,3], carbamazepine, 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 (intracoronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidiner, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terlipressin, terodiline, terfenadine, thioridazine, vandetanib
Herbal preparations/ medications	Herbal preparations/medications known as strong inducers or inhibitors of CYP3A4/5 or those with a known risk of QT prolongation are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

Category	Drug Name
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, 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 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] Source: www.qtdrugs.org (as of Apr 7, 2015)

[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.

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, isavuconazolef, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein, lersivirine, lopinavir[5], modafinil, nafcillin, telotristat
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, apixaban, aprepitant, atorvastatin, avanafil, bosutinib, brotizolam, budesonide, buspirone, cobimetininb, darifenacin, dasatinib, ebastine, eletriptan, eplerenone, everolimus, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, lumefantrine, lurasidone, maraviroc, midazolam, 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, valinomycin, 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, olanzapine, osimertinib, oxytocin, paliperidone, palonosetron, panobinostat, 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, vardenafil, ziprasidone
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan and varencicline
OCT1/2 substrates[4]	Amantadine, 6-beta-hydroxycortisol, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxyplatin, 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, and sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax

[1] Sensitive substratesincludes 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 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 is prohibited when combined with ritonavir (see Table 14-1)

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

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Glossary

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

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 2 and the definition of best response in Section 3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

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.

2.1 Definitions

2.1.1 Disease measurability

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

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 3.2.8.

Measurable lesions (both nodal and non-nodal)

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

- Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 3.2.8.

2.2 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment. Existing bone scans can be used if assess up to 56 days prior to C1D1.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. 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.
- 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.
- Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated 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.

2.3 Baseline documentation of target and non-target lesions

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

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 2.1.1.
- **Nodal target:** See Section 2.1.1.

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

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

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 2-1) and non-target lesions (Table 2-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 2-3) as well as the presence or absence of new lesions.

2.4.1 Follow-up and recording of lesions

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

2.4.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are 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.

2.4.1.2 Nodal lesions

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

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

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

2.4.2 Determination of target lesion response

Table 2-1 Response criteria for target lesions

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

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. Methodology change See Section 2.2.

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 2-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.

- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

2.4.3 Determination of non-target lesion response

Table 2-2 Response criteria for non-target lesions

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

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

Notes on non-target lesion response

- 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 any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).

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

2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.

2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 2-3.

Table 2-3 Overall lesion response at each assessment

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

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 2.4.

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

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

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.

3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

3.1 Best overall response

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

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

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

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

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

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

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

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 investigator review of 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.

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 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).

3.2 Time to event variables

3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that

randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

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

3.2.2 Overall survival

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

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

3.2.3 Time to progression

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

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

3.2.4 Time to treatment failure

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

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

3.2.5 Duration of response

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

risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

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

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

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.

3.2.6 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 3.2.5. 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.

3.2.7 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.

Start dates

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

For the calculation of duration of response the following start date should be used:

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 3.2.8).

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

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

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 3-1.

Table 3-1 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 2.4.

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

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

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

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

3.2.9 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 3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 3-2 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
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 3.2.7.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 3.2.7.
3. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

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

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

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

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

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 3-2 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.

4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

4.1 Study/project specific decisions

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

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

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 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 decision
- Death
- 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)

4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

4.4 Medical validation of programmed overall lesion response

As RECIST 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), these UNK assessments may be re-evaluated by clinicians 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.

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days).

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

4.5.2 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

4.5.5 Study/project specific programming

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

4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 3-2)
- 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 3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor 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.

5 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

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

14.3 Appendix 3: Patient reported outcomes

Figure 14-1 EORTC-QLQ-C30

GERMAN

EORTC QLQ-C30 (version 3.0)

Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine "richtigen" oder "falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Bitte tragen Sie Ihre Initialen ein: _ _ _ _

Ihr Geburtstag (Tag, Monat, Jahr): _ _ _ _ _ _

Das heutige Datum (Tag, Monat, Jahr): 31 _ _ _ _ _ _

	Überhaupt nicht	Wenig	Mäßig	Sehr
1. Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen)?	1	2	3	4
2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:

	Überhaupt nicht	Wenig	Mäßig	Sehr
6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8. Waren Sie kurzatmig?	1	2	3	4
9. Hatten Sie Schmerzen?	1	2	3	4
10. Mussten Sie sich ausruhen?	1	2	3	4
11. Hatten Sie Schlafstörungen?	1	2	3	4
12. Fühlten Sie sich schwach?	1	2	3	4
13. Hatten Sie Appetitmangel?	1	2	3	4
14. War Ihnen übel?	1	2	3	4
15. Haben Sie erbrochen?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
16. Hatten Sie Verstopfung?	1	2	3	4
17. Hatten Sie Durchfall?	1	2	3	4
18. Waren Sie müde?	1	2	3	4
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21. Fühlten Sie sich angespannt?	1	2	3	4
22. Haben Sie sich Sorgen gemacht?	1	2	3	4
23. Waren Sie reizbar?	1	2	3	4
24. Fühlten Sie sich niedergeschlagen?	1	2	3	4
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

Figure 14-2: EORTC-QLQ-BR23

EORTC QLQ - BR23

Patienten berichten manchmal die nachfolgend beschriebenen Symptome oder Probleme. Bitte beschreiben Sie, wie stark Sie diese Symptome oder Probleme während der letzten Woche empfunden haben.

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
31. Hatten Sie einen trockenen Mund?	1	2	3	4
32. War Ihr Geschmacksempfinden beim Essen oder Trinken verändert?	1	2	3	4
33. Schmerzten Ihre Augen, waren diese gereizt oder tränten sie?	1	2	3	4
34. Haben Sie Haarausfall?	1	2	3	4
35. Nur bei Haarausfall ausfüllen: Hat Sie der Haarausfall belastet?	1	2	3	4
36. Fühlten Sie sich krank oder unwohl?	1	2	3	4
37. Hatten Sie Hitzewallungen?	1	2	3	4
38. Hatten Sie Kopfschmerzen?	1	2	3	4
39. Fühlten Sie sich wegen Ihrer Erkrankung oder Behandlung körperlich weniger anziehend?	1	2	3	4
40. Fühlten Sie sich wegen Ihrer Erkrankung oder Behandlung weniger weiblich?	1	2	3	4
41. Fanden Sie es schwierig, sich nackt anzusehen?	1	2	3	4
42. Waren Sie mit Ihrem Körper unzufrieden?	1	2	3	4
43. Waren Sie wegen Ihres zukünftigen Gesundheitszustandes besorgt?	1	2	3	4

Während der letzten vier Wochen:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
44. Wie sehr waren Sie an Sex interessiert?	1	2	3	4
45. Wie sehr waren Sie sexuell aktiv? (mit oder ohne Geschlechtsverkehr)?	1	2	3	4
46. Nur ausfüllen, wenn Sie sexuell aktiv waren: Wie weit hatten Sie Freude an Sex?	1	2	3	4

Bitte wenden

GERMAN

Während der letzten Woche:	**Überhaupt nicht**	**Wenig**	**Mäßig**	**Sehr**
47. Hatten Sie Schmerzen in Arm oder Schulter?	1	2	3	4
48. War Ihr Arm oder Ihre Hand geschwollen?	1	2	3	4
49. War das Heben oder Seitwärtsbewegen des Arms erschwert?	1	2	3	4
50. Hatten Sie im Bereich der betroffenen Brust Schmerzen?	1	2	3	4
51. War der Bereich Ihrer betroffenen Brust angeschwollen?	1	2	3	4
52. War der Bereich der betroffenen Brust überempfindlich?	1	2	3	4
53. Hatten Sie Hautprobleme im Bereich der betroffenen Brust (z.B. juckende, trockene oder schuppende Haut)?	1	2	3	4