NOVARTIS

Clinical Development

LEE011 (ribociclib)

Protocol CLEE011F2301 / NCT02422615

MONALEESA-3: A randomized double-blind, placebo-controlled study of ribociclib in combination with 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

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List of abbreviations

AE	Adverse Event
(e)PRO	(electronic) Patient Reported Outcomes
AI	Aromatase Inhibitors
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BC	Breast Cancer
BIRC	Blinded independent review committee
BPI-SF	Brief Pain Inventory – Short Form
BSEP	Bile salt export pump
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Ratio
CCND1	Cyclin D1
CDK4/6	Cyclin-Dependent Kinases 4 and 6
Cmax	Peak blood concentration
Cmin	Minimum concentration
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
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer's core quality of life questionnaire
EOT	End of Treatment
EQ-5D	EuroQol 5 Dimension questionnaire
ER	Estrogen Receptor
[redacted]	[redacted]
FAS	Full Analysis Set
FFPE	Formalin-Fixed, Paraffin-Embedded
FIH	First-in-human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice

GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HDL	High Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR	Hazard ratio
HR+	Hormone Receptor Positive
IB	Investigator Brochure
IC50	Inhibitory Concentration, where 50% inhibition is observed
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MBC	Metastatic Breast Cancer
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NSAI	Nonsteroidal Aromatase Inhibitors
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
PFS	Progression free survival
P-gP	Permeability-glycoprotein
PgR	Progesterone receptor
PHI	Protected Health Information
PhRMA	Pharmaceutical Research and Manufacturers of America
PK	Pharmacokinetics
PPS	Per Protocol Set
pRb	Retinoblastoma Protein
PS	Performance Status
QD	Quaque Die (every day)

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
R Value	ALT/ALP in x ULN
SAE	Serious Adverse Event
SC	Steering Committee
SD	Stable disease
SEC	Safety Event Categories
SERM	Selective ER Modulators
S-ICF	Study ICF
SMT	Novartis Safety Management Team
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	The elimination half-life associated with the terminal slope (□z) of a semi logarithmic concentration-time curve (time).
TBIL	Total Bilirubin
TTR	Time to Response
ULN	Upper Limit of Normal

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
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
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
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.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
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 a patient permanently discontinues study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.

Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Amendment 2 (28-Jul-2016)

Amendment rationale

Study CLEE011F2301 was initiated in June 2015 and enrollment has been completed on June 14th. 727 patients have been randomized in the study.

The purpose of this amendment is to:

(i). Eliminate the originally planned futility interim analysis:

Since the start of Study CLEE011F2301, additional clinical data have been generated with LEE011 and other CDK 4/6 inhibitors that provide additional assurance of the activity of this compound and class in patients with breast cancer. In addition, Study CLEE011F2301 will be fully enrolled prior to the time of the originally planned futility analysis, negating the need for the originally planned interim futility analysis.

(ii) Eliminate the originally planned efficacy interim analysis and add the requirement of minimum amount of information from 1st line patients in the primary end point final analysis:

The primary objective of the study is to compare investigator assessed PFS in the overall population (both 1st line and 2nd line). If the primary analysis is statistically significant, treatment effect will be evaluated in 1st line and 2nd line patients separately. Based on the estimated median PFS and proportion of patients in 1st line and 2nd line respectively, it is expected that the accumulation of events in 1st line will be slower than 2nd line patients . By the projected efficacy interim analysis, there may not be enough events from 1st line patients to support the treatment effect in this sub population. Hence the originally planned efficacy interim analysis is eliminated. In addition, to ensure enough information coming from the 1st line patients, a requirement of minimum amount of events coming from 1st line patients in the final analysis is added.

(iii). Change the approach for Blinded Independent Review Committee (BIRC) assessment of PFS from a full read to an audit (sample) based approach:

For studies with local PFS as the primary endpoint, central PFS has generally been used as a secondary analysis in support of the treatment effect observed in the primary efficacy analysis. Although, 100% central review of scans has been performed in many trials, there is a growing body of evidence that an audit based approach for central evaluation is sufficient (Zhang et al, 2012, FDA ODAC 2012). Therefore, the study is being amended to change the central assessment of PFS from a full read to an audit based approach. Consequently, blinded independent review committee (BIRC) based PFS will no longer be a secondary endpoint but will be considered supportive of the primary analysis.

[redacted]

Additional changes in the protocol amendment

(i). Clinical pharmacokinetic data has been updated as new data is available

(ii). Clarifications have been provided on the following study procedures:

- Schedule of the EOT visit
- Palliative radiotherapy, previously only allowed for bone pain relief, is permitted provided it is not delivered to a target lesion
- The use of the randomization date as the reference for the tumor assessement schedule

(iii) To better evaluate treatment effect on ORR, a sensitivity analysis of ORR is added for patients with measurable disease at baseline.

(iv) The PK analysis was updated to only summarize PK concentrations by time point considering that PK parameters will not be estimable due to the sparse PK sampling schedule. PK data collected from this study may be used in population PK analysis of ribociclib using non-linear mixed effect modeling and would be reported in a separate report.

(v). The protocol appendix 2 has been updated to reflect the new Novartis guidance on the implementation of RECIST 1.1

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.

- Summary section of the protocol has been updated to maintain consistency within the main body of the protocol
- Section 1.2.1.2.3 has been updated to add new pharmacokinetic data on ribociclib
- Section 3, Table 3-1 secondary and [redacted]
  - to remove the PFS assessed by BIRC as secondary objective [redacted]
  - to clarify the pharmacokinetic endpoint
- Section 4.1.2 has been updated to clarify when an end of treatment (EOT) visit must be performed
- [redacted]
- Section 4.2 and Section 4.3 have been updated to remove the 1st and 2nd interim analyses (respectively futility and efficacy analysis) for the primary endpoint PFS
- Section 6.5.1.3 has been updated to clarify that all QTcF grade values refer to the average of triplicate measurements
- Section 6.6.1.3 has been updated to remove the requirement of palliative radiation solely for bone pain
- [redacted]
- [redacted]

- Section 7.2.1.1 has been updated
  - to reflect the change to the audit based stratefy for the BIRC assessment
  - to clarify that the randomization is the reference date for the planning of the tumor assessment schedule.
- [redacted]
- Section 7.2.1.3 has been added to describe the describe the audit-based central assessment
- Section 8.6 has been updated to reflect the removal of the 1st and 2nd interim analyses (respectively futility and efficacy analysis) for the primary endpoint PFS
- Section 10, 10.5.1, 10.7.1 has been updated to reflect the removal of the 1st and 2nd interim analyses (respectively futility and efficacy analysis) for the primary endpoint PFS
- Section 10.4.4 has been updated to describe the supportive analysis of PFS using audit based BIRC assessment
- Section 10.5 has been updated to remove reference to the BIRC based PFS as secondary endpoint
- Section 10.5.2.1 has been removed to reflect the removal of the PFS as assess by the BIRC as a secondary endpoint
- Section 10.5.2.2 has been updated to add a sensitivity analysis for Overall Response Rate (ORR)
- Section 10.5.4 has been updated to reflect the change in the analysis of PK data
- [redacted]
- Section 10.7.2 to reflect the removal of one OS interim analysis at the originally planned PFS efficacy interim analysis
- Section 10.8 has been updated
  - to reflect the removal of one OS interim analysis at the originally planned PFS efficacy interim analysis
  - to add the requirement of minimum amount of information coming from 1st line patients in final analysis.
  - to add sample size calculation for audit size of sample-based BIRC assessment of PFS.
- Section 13: new protocol references have been added
- Appendix 2 has been updated to reflect the new Novartis guidance on the implementation of RECIST 1.1
- In addition to above, changes to typographical errors where applicable have been made.

IRBs/IECs

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

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

Amendment 1

Amendment rationale

Study CLEE011F2301 was initiated in June 2015 and enrollment is currently ongoing.

As of February 17th 2016, 351 patients have been randomized in the study.

The purpose of this amendment is to:

(i) Update and clarify the safety monitoring of patients to be consistent across ribociclib clinical trials, and better characterize the QTc and liver side effects, including:

- Management of QTcF prolongation:

Potential risk of QT prolongation has been observed in patients treated with ribociclib. Updates to inclusion and exclusion criteria, ECG monitoring (triplicates) and dose modification guidelines for QTcF prolongation have been made.

- Management of hepatic toxicities:

Recent data suggests a potential risk of hepatic toxicity (drug induced liver injury [DILI] indicated by an increase of transaminases, in isolation or with bilirubin increase) in patients treated with ribociclib. Updates to monitoring and dose adjustment guidelines for hepatobiliary toxicities including ALT, AST and total bilirubin have been added and separated from the dose modification guidance for other adverse events. Additional blood collections for laboratory assessments to further characterize potential drug-induced liver injury, including immunological markers (e.g. immunoglobulins, C-reactive protein, autoimmune hepatitis markers) and total bile acids as part of clinical safety assessments, [redacted]

- Management of dose modification based on local laboratory results:

Clarification was provided that, in case of safety emergency, local laboratories results can be used to evaluate the need for potential study treatment dose modifications.

(ii).Modification of the study population and eligibility criteria:

Following interaction with Health Authorities, men are eligible to be included in the study.

(iii)Additional changes

- Revision of the screening visit window changed within 21 days to within 28 days of randomization
- Whole body bone scan window has been changed from within 28 days to within 42 days of randomization
- Removal of the requirement for a central radiology assessment by medical oncologist: Medical oncologist review has been replaced by a standard blinded independent review committee (BIRC) review assessment.
- List of prohibited concomitant medications has been updated based on recently released internal Oncology Clinical Pharmacology drug-drug interaction guidance

(from 2015) and based on new data and recommendations from the latest version of LEE011 Investigator's Brochure.

- Increase blood volume for circulating tumor DNA from 10mL to 20mL at Cycle 1 Day 1 to identify and validate a gene mutation signature that may predict response and efficacy using multiplexed approach such as next generation sequencing.
- In the initial rat ADME study cited in previous IB version, thyroid had the highest exposure in albino animals only. As a precaution, thyroid function was monitored in all clinical study protocols. A most recent study (DMPK 1300792) using p.o. dosing in partially pigmented animals with a longer observation period showed the highest distribution to the melanin-containing structures and not to the thyroid gland. In addition, no clinically significant thyroid adverse events have been reported in clinical trials so far. Based on this information, the risk to thyroid gland is removed from the reference safety information for the compound and thyroid laboratory monitoring in clinical protocols are no longer mandated.
- Update of the protocol requirements for consistency with the most recent IB information:
  - New information is provided on the safety pharmacology and toxicology
  - Update clinical trial information with the most recent data
- Minor editorial changes, typographical error corrections, additional clarifications to address investigators' questions and alignment to the most recent program standard language as described in the list of changes below.

Changes to the protocol

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

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

- Summary section of the protocol has been updated to maintain consistency within the main body of the protocol
- Section 1.1 Addition of disease information regarding the men population
- Section 1.1.2 Addition of most recent information on available therapeutic options
- Section 1.2 Addition of language to refer to most recent version of the ribociclib investigator brochure
- Section 2.3 and 2.5 have been updated to incorporated most updated trials information
- [redacted]
- Section 4 and Figure 4-1 have been updated to incorporate men population and screening visit window of 28 days into the study design
- Section 4.1 Advanced/ metastatic terms have been included to add clarity to the patient population in the stratification criterion
- Section 5.1 Patient population has been updated to reflect the inclusion of men in the study.

- Section 5.2 Inclusion Criteria has been updated:
  - #1) Addition of male population and male contraception information
  - #2) to clarify that ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) are not allowed for induction of ovarian suppression in this study.
  - #3) and 4) to clarify that diagnosis of breast cancer should be based on recent biopsy
  - #6) to clarify the definition of curative therapy per protocol. Advanced/ metastatic terms have been included to add clarity to the patient population. The terms relapse and progressed have been corrected accordingly to the treatment setting.
  - #8) phosphorus assessment has been removed from screening visit.
- Section 5.3 Exclusion Criteria have been updated:
  - #12) to clarify that squamous cell carcinoma refers to squamous skin cancer.
  - #17). and #18):
    - To clarify the exclusion criteria for patients with clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality and for patients currently receiving prohibitied medications.
    - To clarify that resting heart rate should be <90 bpm
- Section 6.1 has been updated with timing recommendation on dosing schedule and meal conditions
- Section 6.5.1.2:
  - To add clarity on fulvestrant dosing interruption
  - To add clarity on the use of local laboratories results for dose modifications.
  - To add clarity on dose modification guidelines
- Section 6.5: Table 6-5 and Table 6-6
    - Section 6.5.1.2 wording has been modified to clarify to the dosing recommendations and requirements
    - Dose modifications have been updated to clarify actions to be taken for hematologic toxicities, QTcF prolongation and all other toxicities, as well as providing new guidelines for hepatic toxicities.
    - Renal toxicity wording has been moved from section 6.5.1.3.2 to the safety section 6.5.1.3.1 for clarity.
    - “Placebo” has been added in the table wording and baseline value has been modified to baseline grade based on CTCAE.
- Section 6.6.2.1 and 6.6.3: the use of corticosteroids therapy has been added to allow the topical and short term use per protocol. Chronic use remain prohibited due to the potential for drug- drug-interaction.
- Section 6.6.2 immunosuppressant therapies have been added in the medications to use with caution due to their higher risk of infections.
- Section 6.6.4 has been added to clarify the use of medications with a known risk of QT prolongation

- Section 7, Table 7-1:
  - Modification to the screening window change within 21 days to within 28 days of randomization.
  - Modification to the visit windows schedule to include a ±3 days visit windows for all visits including PK visits
  - To add clarity that physical exam assessment will not be repeated at Cycle 1 Day 1 when done in the timeframe -7 to -1 at the screening visit
  - [redacted]
  - Revision to the whole body bone scan requirement window: change from 28 to within 42 days or 6 weeks prior to randomization.
- Section 7.1.1 screening:
  - clarification that screening assessments to be performed at -7 to -1 should be repeated in the case where randomization visit is delayed more than 7 days from cycle 1 day 1.
  - clarification on inform consent form process for patients who rescreen
- Section 7.1.3
  - Clarity added by the addition of the word "reasonable"
  - update to the study treatment discontinuation language in the case of AEs.
- Section 7.2.1.1
  - Revision of window regarding whole body bone scan: change from within 28 days to within 42 days of randomization
  - Updated to remove the medical oncologist review of central images.
- Section 7.2.2: Thyroid monitoring has been removed as is not longer mandatory based on recent study results.
- Section 7.2.2.5:
  - clarification on the use of local laboratories results
  - [redacted]
- [redacted]
- Section 7.2.2.6.1 and Table 7-5:
  - Electrocardiogram (ECG) was updated with the use of triplicate for each collection time points
  - Clarity was added on the unscheduled ECG management
- Section 7.2.3.1: clarification to PK sampling when no study drug has been taken
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- Section 7.2.6 Table 7-9 has been updated to reflect the 28 days screening visit window

- Section 8: implementation of new Serious Adverse Event (SAE) reporting instructions
- Section 8.4: addition of pregnancies recommendations for female partner of any male participants
- [redacted]
- Section 13: new protocol references have been added
- Section 14.1 Appendix 1- Concomitant medications
  - Table 14-1 and Table 14-2 have been updated with the latest information available.
  - Modification to the table removing CYP2D6 since is it not applicable to the study treatment .
- In addition to above, changes to typographical errors where applicable have been made.

Review requirements by IRB/IEC and Heath Authorities

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

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

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

Protocol summary:

Title	A randomized double-blind, placebo-controlled study of ribociclib in combination with 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
Brief title	Study assessing the efficacy and safety of ribociclib plus fulvestrant in men and postmenopausal women with advanced breast cancer having been treated with no or only one prior endocrine therapy.
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Treatment of hormone receptor (HR) positive, HER2-negative breast cancer still represents an unmet medical need as a significant number of patients are expected to have, or to develop, resistance to endocrine therapies that have been given in the adjuvant or first line metastatic setting. CDK4/6 pathway alterations appear to play a key role in the development of this resistance. The rationale for assessing the efficacy of ribociclib, a CDK4/6 inhibitor, in combination with the hormonal agent fulvestrant, in a randomized Phase III study is therefore based upon the role of the CDK4/6 pathway in HR+ breast cancer and the potential synergy when combined with hormonal agents such as fulvestrant. The purpose of this study is to determine whether treatment with ribociclib plus fulvestrant will result in an improved progression free survival compared to fulvestrant and placebo in men and postmenopausal women with HR+, HER2-negative advanced breast cancer who have received no or only one prior endocrine treatment for advanced disease.
Primary Objective(s)	The primary objective is to compare progression free survival (PFS) between ribociclib in combination with fulvestrant to placebo in combination with fulvestrant among men and postmenopausal women with HR+, HER2-negative advanced breast cancer who received no or only one prior endocrine treatment for advanced disease.
Secondary Objectives	● To compare the two treament arms with respect to overall survival ● ● To evaluate the two treatment arms with respect to overall response rate, clinical benefit rate, time to response and duration of response as assessed by tumor evaluation (RECIST 1.1) every 8 or 12 weeks. ● To evaluate the two treatment arms with respect to time to deterioration of ECOG performance status by assessing the performance status at each cycle. ● To evaluate the safety and tolerability of ribociclib in combination with fulvestrant by assessing the frequency/severity of adverse events (AEs) and of laboratory abnormalities on a continuous basis throughout the study. ● To evaluate patient reported outcomes every 8 or 12 weeks for health-related quality of life (QOL) in the two treatment arms based on the global health status/QOL scale of the EORTC QLQ-C30 questionnaire. ● To characterize the pharmacokinetics (PK) of ribociclib (and relevant metabolites such as LEQ803) at Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 2 Day 15, when given in combination with fulvestrant by compiling summary statistics for PK parameters at steady state.

Study design	This is a randomized, phase III, double-blind, global trial comparing the combination of fulvestrant + ribociclib to fulvestrant + placebo in men and postmenopausal women with HR+, HER2-negative advanced breast cancer. The study will consist of a 28-day screening phase, of a treatment phase, and of a post-treatment phase which includes safety, efficacy, and survival follow up. Patients will be randomly assigned to either fulvestrant+ribociclib or fulvestrant+placebo in a 2:1 ratio. Randomization will be stratified by the following factors: ● Lung or liver metastases (yes versus no) ● Previous endocrine therapy
Population	The study will include 660 men and postmenopausal women with HR+ HER2-negative advanced breast cancer who received no or only one prior endocrine therapy. The investigator or designee must ensure that only patients who meet all of the following inclusion and none of the exclusion criteria are offered treatment in the study.
Inclusion criteria	Refer to Section 5.2 for details on and full listing of 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 ● Patient is a man or a postmenopausal woman ● Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer ● Patient has HER2-negative breast cancer ● Patient must have either: ● Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1. OR ● If no measurable disease is present, then at least one predominantly lytic bone lesion must be present ● Patient has advanced (loco regionally recurrent not amenable to resection or radiation therapy with curative intent or metastatic) breast cancer. Patients may be : ● newly diagnosed advanced/metastatic breast cancer, treatment naïve ● relapsed with documented evidence of relapse more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced/metastatic disease ● relapsed with documented evidence of relapse on or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced/metastatic disease ● relapsed with documented evidence of relapse more than 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor) for advanced/metastatic disease ● newly diagnosed advanced/ metastatic breast cancer, that progressed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor) ● Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 ● Patient has adequate bone marrow and organ function

Exclusion criteria	Refer to Section 5.3 for details on and full listing of exclusion criteria. ● Patient with symptomatic visceral disease ● Patient has received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant or any CDK4/6 inhibitor ● Patients with Child pugh score B or C ● Patient with inflammatory breast cancer at screening or concurrent malignancy or malignancy within 3 years of randomization ● Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following: ● History of angina pectoris, symptomatic pericarditis, coronary artery bypass graft (CABG) or myocardial infarction within 6 months prior to study entry ● Documented cardiomyopathy ● Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) ● 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 medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug) • Inability to determine the QTcF interval • Clinically significant cardiac arrhythmias including but not limited to (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third degree AV block) ● Systolic Blood Pressure (SBP) >160 or <90 mmHg ● Bradycardia (heart rate < 50 bpm at rest), by ECG (mean of triplicate) and pulse. • Tachycardia (heart rate > 90 bpm at rest), by ECG (mean of triplicate) and pulse. ● On screening, inability to determine the QTcF interval on the ECG (ie: unreadable or not interpretable) or QTcF >450 msec (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs). ● Patient has not recovered from all toxicities related to prior anticancer therapies to NCI CTCAE version 4.03 Grade ≤1 ● Patient has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization ● 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 ● 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. ● Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to start the treatment: ● Known strong inducers or inhibitors of CYP3A4/5. ● Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.

<table>
<tr><td></td><td>● Herbal preparations/medications, dietary supplements (except vitamins)</td></tr>
<tr><td>Investigational and reference therapy</td><td>For this study, the term “investigational drug” refers to Novartis study drug ribociclib. Fulvestrant is also being used in this study. Study treatment in this study refers to the combination of drugs in each of the study arms and includes ribociclib/placebo and fulvestrant.
Patients will be randomly assigned to one of the below treatment arms in a 2:1 ratio:
● Experimental arm (Arm A): fulvestrant + ribociclib
OR
● Control arm (Arm B): fulvestrant + placebo

<table><tr><th>Study treatment</th><th>Pharmaceutical form and route of administration</th><th>Frequency and/or Regimen</th></tr><tr><td>Fulvestrant</td><td>Two 5ml injections for i.m. administration</td><td>Dosed every 28 days (Cycle n Day 1) with 1 additional dose on Day 15 of Cycle 1</td></tr><tr><td>Ribociclib/ placebo</td><td>Capsule for oral use</td><td>Once daily; days 1 to 21 in a 28-day Cycle</td></tr></table></td></tr>
<tr><td>Efficacy assessments</td><td>● CT/ MRI every 8 weeks for the first 18 months, then every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision
● Brain CT or MRI as clinically indicated if brain lesion at screening
● Whole body scan as clinically indicated
● Bone X-ray, CT or MRI (if bone lesion at screening) every 8 weeks for the first 18 months and then every 12 weeks thereafter
● Skin color photography (if skin lesions at screening) every 8 weeks during the first 18 months and then every 12 weeks thereafter
● CT/ MRI for any disease outside of the chest, abdomen, pelvis (if lesion identified at screening) every 8 weeks for the first 18 months and then every 12 weeks thereafter
● Survival status every 12 weeks (or earlier if required) regardless of treatment discontinuation reason</td></tr>
<tr><td>Safety assessments</td><td>● Physical examinations
● ECOG performance status
● Height, weight, and vital signs
● 12 lead ECGs
● ECHO, MUGA scan
● Laboratory assessments including hematology, biochemistry, lipid panel, coagulation (via INR), [redacted], and urinalysis</td></tr>
<tr><td>Other assessments</td><td>Pharmacokinetic: PK blood samples will be collected for analysis of ribociclib (and metabolites) plasma concentrations [redacted]

Patient-reported outcomes: Patient questionnaires (EORTC-QLQ-C30, EQ-5D-5L, BPI-SF) will be collected to assess health-related quality-of-life, health status, functioning, disease symptoms, side effects, and cancer-related pain.
[redacted]</td></tr>
</table>

	[redacted]
Data analysis	The primary objective for this study is to determine whether treatment with fulvestrant + ribociclib prolongs PFS compared to treatment with fulvestrant + placebo in men and postmenopausal women with HR+, HER2-negative advanced breast cancer. The primary efficacy endpoint, PFS, will be determined based on local tumor assessment following RECIST 1.1 guidelines. The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups using a stratified (randomization strata per IRT) log-rank test at one-sided 2.5% level of significance. Distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented for each of the two treatment groups. The stratified Cox regression will be used to estimate the hazard ratio (HR) of OS, along with 95% confidence interval. Subgroup analyses will be performed on each level of stratification factors if the primary analysis is significant. The analysis will include Kaplan-Meier summaries and estimation of hazard ratios from un-stratified Cox regression models. Additional subgroup analyses to assess the homogeneity of treatment effect based on demographic and baseline disease characteristics may be performed. The Full Analysis Set (FAS) will comprise all randomized patients. Following the intent to treat (ITT) principle, patients will be analyzed according to the treatment and strata they have been assigned to at the time of randomization. The FAS will be the primary population for all efficacy analyses. The Safety Set includes all patients who received at least one dose of study medication defined as fulvestrant, or ribociclib/placebo and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment actually received. One of the secondary objectives of the study is to determine whether treatment with fulvestrant + ribociclib prolongs overall survival (OS) compared to treatment with fulvestrant + placebo. OS will be hierarchically tested (provided the primary PFS analysis is statistically significant), in the following way. The first potential time point for OS analysis will be at the time of the primary PFS analysis at which time approximately 161 deaths are expected. If OS is not statistically significant at this stage, the 2nd OS analysis is planned after approximately 263 deaths are expected. If OS is not statistically significant at this stage, the final OS analysis will be planned after approximately 351 deaths
Key words	HR-positive, HER2-negative, advanced breast cancer, ribociclib, fulvestrant, CDK4/6, Phase III, ER-positive, PR-positive, postmenopausal, men, metastatic breast cancer

1 Background

1.1 Overview of disease pathogenesis and current treatment

1.1.1 Epidemiology

An estimated 231,840 new cases of invasive breast cancer are expected to be diagnosed among women in the US during 2015; excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women. An estimated 40,730 breast cancer deaths (40,290 women) are expected in 2015. Breast cancer ranks second as a cause of cancer death in women after lung cancer (Cancer facts & figures 2015). Breast cancer in men is a less frequent disease than women and makes up < 1% of all cases of breast cancers; its treatment is based on the guidelines for female breast cancer (Foerster 2014, Agrawal 2007, Patten 2013). Subtypes of BC are classified by the presence of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) antigen as well as by distinct gene expression profiles (Perou et al 2000; Sotiriou and Pusztai 2009) and other features for prognostic and treatment purposes. Seventy percent of invasive breast cancers in women > 45 years of age, express ER and/or PgR, but not HER2, and are termed hormone receptor positive (HR+, HER2-negative) (Huang 2005).

1.1.2 Available therapeutic options in ER+, HER2-negative breast cancer

Estrogen deprivation therapy is the core treatment modality in patients with HR+ advanced BC.

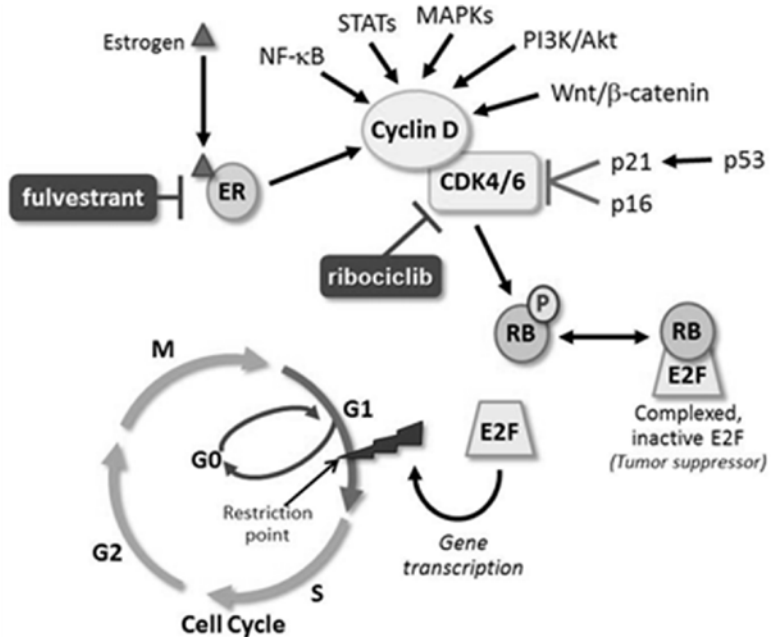
Endocrine therapy options for postmenopausal women with ER+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer) include selective ER modulators (SERM; for example, tamoxifen), ER antagonists (for example fulvestrant), selective nonsteroidal aromatase inhibitors (NSAI; anastrozole and letrozole) and steroidal aromatase inhibitors (exemestane). Blocking estrogen signaling with tamoxifen has been the main treatment approach for ER+ breast cancer for over 35 years. In postmenopausal women, aromatase inhibitors (AI) reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens in non-ovarian tissues; synthesis in these tissues is the primary source of estrogens in postmenopausal women. AIs are generally used as the first line of therapy for women with HR+ breast cancer (Beslija 2009; NCCN 2.2015). Fulvestrant is a pure ER antagonist approved at the dose of 500mg for the treatment of postmenopausal HR+ BC women previously treated with antiestrogen (Di Leo 2010; Di Leo 2014). Recently, the phase 2 FIRST trial (Robertson 2014) showed that the use of fulvestrant in first line setting significantly prolonged PFS as compared to anastrozole (median TTP 23.4 months versus 13.1 months (HR 0.66; 95% CI:0.47, 0.92; p=0.01)) and extends OS (54.1 months versus 48.4 months (HR 0.70; 95% CI: 0.5, 0.98; p=0.04)) (Ellis 2015). The combination of targeted and endocrine therapies has also been evaluated: everolimus, an mTOR inhibitor, combined with exemestane showed synergistic inhibition of the tumor proliferation and is approved for postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole (Baselga 2012); recently, palbociclib, a CDK4/6i, has been approved

in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease based on the results of the phase 2 Paloma-1 study. The addition of palbocicib to letrozole significantly prolonged PFS as compared to letrozole alone (median PFS 20.2 months versus 10.2 months (HR 0.49; 95% CI:0.32, 0.75; p=0.0004)) (Finn 2015). Palbociclib in combination with fulvestrant for the treatment of patients with HR+ Her 2 advanced breast cancer who relapsed or progressed during prior endocrine therapy, resulted in prolonged progression free survival. (median PFS was 9.5 months for palbociclib plus fulvestrant versus 4.6 months for the fulvestrant – placebo (HR 0.46; 95% CI: 0.36 - 0.59; P:<0.001)). In this study, women were eligible regardless of their menopausal status and up to 1 line of prior chemotherapy in the context of advanced disease was allowed. (Cristofanilli M 2015, Turner 2015)

1.1.3 Role of the CDK4/6 pathway in breast cancer

Studies of ER+ breast cancer cell lines indicate that estrogens and antiestrogens act on sensitive populations of cells in early to mid-G1 phase (Leung 1987). G1/S transition is under the control of cyclin dependent kinases (CDKs) which are activated by specific complex formation with regulatory cyclins. CDK4 and CDK6 are activated by binding to D-type cyclins and act early in G1 phase (Sherr 1999; Musgrove et al 2011). A primary target of CDK4/6 activation in G1 phase is the retinoblastoma protein (pRb), which mediates G1 arrest through sequestration of transcriptional factors of the E2F-DP family. Phosphorylation of pRb and other members of the pocket protein family (p107 and p130) by active cyclin-CDK complexes leads to release of E2F and DP and subsequent transcription of genes requisite for entry into the S-phase (Weinberg 1995). D-type cyclins play an essential role in the recognition of extracellular growth stimuli and initiation of G1 to S transit (Roussel 1995; Sherr 1995).

Figure 1-1 Regulation of cell cycle checkpoint control



Adapted from (Lange and Yee 2011)Dysregulation of cell cycle checkpoints is common in cancer and aberrations in the cyclin/CDK/pRb pathway are frequently observed in breast cancer. Such aberrations include amplification of cyclin D1 and CDK4 along with loss of CDKN2A which encodes $p16^{INK4a}$, an endogenous CDK inhibitor, all of which lead to activation of the cyclin/CDK/pRb pathway (Holm et al 2012; The Cancer Genome Atlas Network 2012; Beroukhim et al 2010). An upstream role for cyclin D1 has also been suggested by recent reports describing direct physical interactions between cyclin D1 and the ER, leading to recruitment of steroid receptor coactivators and activation of ER-dependent transcription. This occurs in the absence of hormone and is independent of D cyclin association with CDK4 (Neuman 1997; Zwijsen 1997; Zwijsen 1998; McMahon 1999). Furthermore, recent preclinical data suggest that despite estrogen deprivation, ERα retains genomic activity and drives a CDK4/E2F dependent transcriptional program (Miller 2011).

Previously published data have suggested that CDK4/6 inhibition may play a key role in the treatment of subsets of breast cancers. Loss of pRb has been observed in 10-30% of breast cancer patients (Knudsen and Knudsen 2008), however, this is more commonly seen in ER-negative patients, as evaluated using a gene signature of pRb loss (Ertel et al 2010). Patients with HR+ breast cancer exhibiting a gene expression signature of pRb loss had shorter recurrence-free survival following adjuvant tamoxifen (Bosco et al 2007). A tumor gene expression signature of E2F activation was associated with higher residual tumor cell proliferation following pre-surgical AI therapy. Therefore, activation of the CDK/pRb/E2F axis promotes endocrine resistance, and treatment with a CDK4/6 inhibitor or knockdown of CDK4 expression would be expected to abrogate endocrine-resistant cell proliferation (Caldon 2006).

In vitro data generated from 47 human breast cancer cell lines demonstrated preferential sensitivity to CDK4/6 inhibitors in ER+ cell lines (Finn et al 2009; O'Brien et al 2014). Tumor growth inhibition by CDK4/6 inhibitors has been demonstrated in vivo in preclinical models of endocrine-resistant breast cancer by palbociclib (PD 0332991) (Miller 2011; Thangavel 2011) and in mouse xenograft models of HR+ breast cancer by ribociclib in combination with letrozole or fulvestrant (O'Brien et al 2014). Clinically, palbociclib combined with letrozole showed a benefit prolonging the progression free survival (PFS) in postmenopausal women with ER+/HER2-negative advanced BC (Finn et al 2015) and has recently received accelerated approval based on PFS by the FDA.

In conclusion, targeting the CDK/pRb/E2F pathway via a CDK4/6 inhibitor such as ribociclib in combination with endocrine treatment has the potential to have a positive influence on breast cancer progression.

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

This study includes ribociclib and fulvestrant as treatments.

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 LEE011 (ribociclib) [Investigator Brochure] for details.

1.2.1.1 Nonclinical experience

1.2.1.1.1 Nonclinicalpharmacology of ribociclib

In Jeko-1 mantle cell lymphoma (MCL) cells that overexpress cyclin D1 as a result of the t(11;14) chromosomal translocation, ribociclib 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. Ribociclib doses that induce >75% inhibition of pRb phosphorylation in this model are associated with complete tumor regression (see LEE011 (ribociclib) [Investigator Brochure]). 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 LEE011 (ribociclib) [Investigator Brochure] for more details.

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, LEE011 (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 vivo studies of ribociclib in combination with endocrine therapy have demonstrated increased anti-tumor activity of the combination for letrozole, fulvestrant and tamoxifen compared to single agent ribociclib activity([Investigator Brochure]; O'Brien et al. 2014;) which support the proposed combination.

1.2.1.1.2 Safety pharmacology and toxicology

In vivo cardiac safety studies demonstrated a signal for QT prolongation with the potential to induce incidences of premature ventricular contractions (PVCs) at higher exposure levels.

The effects of LEE011 on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation) and testes (atrophy) are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition.

An increased number of ovarian corpora lutea was observed in a single female dog in the 4-week toxicity study at the highest dose tested (20 mg/kg/day) and this effect could also be related to the pharmacology of LEE011 (arrest of estrous cycle).

The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) and the kidney (concurrent degeneration and regeneration of tubular epithelial cells) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of LEE011.

Inflammatory changes in the lungs of dogs were considered secondary to aspiration of test article and are indicative of the irritant potential of the formulated test-article in the respiratory tract. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver.

Generally all changes demonstrated either reversibility or a clear tendency towards reversibility. In the rat, there was no evidence of teratogenicity however ribociclib was embryofetotoxic. Data from a rabbit embryofetal development study, shows that ribociclib is teratogenic in the rabbit in the absence of maternal toxicity.

1.2.1.1.3 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 (T1/2) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h). Bioavailability was low to moderate in rat (37%) andcynomolgus monkey (17%); moderate in mouse (65%) and dog (64%). Following oral administration, time to reach maximal plasma concentrations (Tmax) 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]LEE011 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. 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.

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.

1.2.1.2 Clinical experience

Ribociclib is currently being investigated in patients as a single agent in 3 phase I studies, in 2 phase II studies and in combination in 15 studies: 12 phase Ib/II studies and 3 randomized phase III studies. Four studies, were closed for enrollment: a randomized phase II study; a phase I dose finding study; a phase I study in malignant rhabdoid tumors and neuroblastomas; and a phase Ib/II study in BRAF mutant melanoma. Ribociclib is also being investigated in 4 clinical pharmacology studies: 3 clinical pharmacology studies in healthy subjects have been completed. Details on ongoing studies can be found in the LEE011 (ribociclib) [Investigator Brochure].

In single agent trials, a total of 199 patients have been treated: 157 in study [CLEE011X2101] as of 15-Jun-2015 (in a Caucasian population, including 85 in the dose escalation), 17 in [CLEE011X1101] as of 28-Jan-2015 (in Japanese patients, all in the dose escalation) and 32 in [CLEE011X2102] as of 9-Apr-2015 (in patients under the age of 21 years, all in the dose escalation).. Please refer to the LEE011 (ribociclib) [Investigator Brochure] for more details.

Ribociclib is being evaluated in a combination with fulvestrant and BKM120 (buparlisib) in an ongoing study [CLEE011X2108] as detailed in Section 1.2.3.

The combination of ribociclib (600 mg) with letrozole (2.5 mg once daily) is being evaluated in an ongoing study [CLEE011A2301]; as of 12-Feb-2015, the study has enrolled 668 patients. The safety of 664 patients was reviewed at the most recent DMC on 07-Oct-2015, with the recommendation to continue the study unchanged.

1.2.1.2.1 Clinical safety of ribociclib

Single agent therapy:

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 weeks 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 (23.5%), thrombocytopenia (23.5%); 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) typically 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. 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 LEE011 (ribociclib) [Investigator 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 LEE011 (ribociclib) [Investigators Brochure] for more details.

1.2.1.2.2 Clinical efficacy of ribociclib

Preliminary anti-tumor activity of ribociclib from an ongoing Phase I 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) LEE011 (ribociclib) [Investigator Brochure]. Stable disease (SD) was the best overall response in 41 (37%) patients. 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

The pharmacokinetics of ribociclib have been evaluated following single and repeat daily doses in the ongoing single agent, phase I study in patients with advanced solid tumors or lymphomas [CLEE011X2101]. Following oral administration of ribociclib, peak plasma concentrations (Cmax) are achieved at approximately 1-4 hours post-dose. Ribociclib plasma exposure (Cmax and AUC0-24h) demonstrates slightly over-proportional increases across the dose range tested (50 to 1200 mg). Steady-state is generally reached by Day 8 and the mean effective T1/2 based on accumulation ratio (i.e., T1/2,acc) ranged from 12.3 to 42.9 hours across the dose range tested. The mean accumulation ratio (Racc) calculated from AUC0-24h at steady-state and AUC0-24h 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 Tmax (n=72) is 2.1 h, and AUC0-24h (n=53) ranges from 6770-90600 ng*h/mL (geometric mean = 23600 ng*h/mL). At this dose, inter-patient variability in Cmax 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 AUC0-24h after single and multiple doses. Refer to the LEE011 (ribociclib) [Investigators Brochure] for more details.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 AUCinf. 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 [14C]AUC0-48h, and 17.9%, 19.8% and 21.6% of ribociclib AUC0-48h, based on metabolite profiles.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 resulting in a 23% decrease in Cmax (geometric mean ratio: 0.775; 90% confidence interval [CI]: 0.700, 0.858) and a median difference in Tmax of 2 hours. However, there was no effect on the

extent of absorption as the overall exposure (AUCinf) 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 Cmax (32%), a delay in median Tmax, and no substantial effect on overall exposure. Results from this study indicate the DiC can be taken without regard to meals. Refer to the LEE011 (ribociclib) [Investigators Brochure] for more details.

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 Cmax and AUCinf by 1.7-fold and 3.2-fold, respectively, following a single oral dose of 400 mg ribociclib. Cmax and AUClast for LEQ803 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 Cmax and AUCinf by 81% and 89%, respectively, following a single oral dose of 600 mg ribociclib. LEQ803 Cmax increased 1.7-fold and AUCinf decreased by 27%, respectively. These results demonstrated that concurrent use of strong CYP3A4 inhibitors or 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 Cmax and AUCinf by 2.1-fold and 3.8-fold, respectively. The effect of multiple doses of ribociclib on caffeine was minimal, with Cmax decreased by approximately 10% and AUCinf increased slightly by 20%. Based on these data, ribociclib (400 mg) is a moderate CYP3A4 inhibitor (≥ 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 LEE011 (ribociclib) [Investigators Brochure] for more details.

1.2.2 Overview of fulvestrant

Fulvestrant is a unique estrogen receptor down regulator with no known agonist effects (Addo et al 2002). Fulvestrant's mechanism of action is distinct from other endocrine agents (Wakeling et al 2000); it binds, blocks and, unlike tamoxifen or other SERMs, degrades the estrogen receptor, completely inhibiting estrogen receptor signaling. As a result, there is less chance of the estrogen receptor being activated by alternative pathways that are believed to cause resistance (e.g. growth factor-mediated mechanisms) (Nicholson et al 2005).

Fulvestrant (FASLODEX®) is a first in class endocrine agent that was approved at the dose of 500mg for the treatment of postmenopausal women with HR+ advanced BC who have failed on prior anti-estrogen therapy. This approval was based on data from the CONFIRM study which demonstrated that 500 mg of fulvestrant showed better progression free survival

compared to 250 mg for postmenopausal women with estrogen receptor–positive advanced breast cancer who experienced progression after prior endocrine therapy (Di Leo 2010; Di Leo 2014). More specifically, in that trial, subgroup analysis showed that PFS was prolonged in patients who had recurred or relapsed during anti-estrogen therapy (median PFS 8.6 vs. 5.8 months; HR 0.76; 95% CI: 0.62-0.94; p=0.013) or during AI therapy although not reaching statistical significance for the latter (median PFS 5.4 vs. 4.1 months; HR 0.85; 95% CI: 0.67-1.08; p=0.195) (FASLODEX® prescribing information). Median OS was 26.4 months for fulvestrant 500 mg and 22.3 months for 250 mg (HR 0.81; 95% CI 0.69–0.96; p=0.02) (DiLeo 2014).

Fulvestrant has also been investigated as a first-line therapy in the phase II, randomized FIRST study (Fulvestrant First-Line Study Comparing Endocrine Treatments) where fulvestrant 500 mg was compared to anastrozole in postmenopausal women with HR+ advanced breast cancer who received no prior endocrine therapy. When 79.5% of patients had discontinued study treatment, the median TTP for fulvestrant was 23.4 months versus 13.1 months for anastrozole (HR 0.66; 95% CI:0.47, 0.92; p=0.01). The best overall response to subsequent therapy and clinical benefit rate for subsequent endocrine therapy were similar (Robertson 2012). Recent median OS data, with analyses conducted at 66.8% maturity showed 54.1 months for fulvestrant and 48.4 months for anastrozole (HR 0.70; 95% CI 0.5-0.98; p=0.041) (Ellis et al 2015, Robertson SABCS abstract 2014). Fulvestrant at the dose of 250 mg has also demonstrated efficacy similar to tamoxifen in the first line setting of HR+ breast cancer tumors (78% of the study population in a preplanned subset analysis) where median TTP was 8.2 months for fulvestrant and 8.3 months for tamoxifen (HR 1.10; 95% CI: 0.89- 1.36; p=0.39) (Howell 2004). The difference in these TTPs for fulvestrant may be attributed to the higher dose of 500 mg since findings from clinical, biological studies and PK modeling suggested that fulvestrant at an increased dose could further increase the clinical efficacy (Robertson 2004). FALCON (Fulvestrant and AnastrozoLe COmpared in hormonal therapy Naïve advanced breast cancer; clinicaltrials.gov identifier: NCT01602380) is a randomized phase III study comparing fulvestrant (500 mg) with anastrozole for postmenopausal women who have not previously been treated with any hormonal therapy in the metastatic setting. This study has completed enrollment in September 2014 and results are still pending.

Clinical safety of fulvestrant

The most common clinically significant adverse reactions occurring in ≥5% of patients receiving fulvestrant 500 mg were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation. Please refer to the local SmPC for pooled safety data for fulvestrant 500 mg data.

1.2.2.1 Clinical pharmacokinetics of fulvestrant

Fulvestrant is slowly absorbed after administration of 500 mg intramuscularly (long-acting formulation). Maximum plasma concentrations are reached after about 5 days. Steady-state is achieved within the first month of dosing, if an additional dose is given 2 weeks after the initial dose. At steady-state there is more than a 2-fold difference between mean Cmax and

Cmin. After intramuscular administration, the exposure is approximately dose proportional in the dose range of 50 to 500 mg. Fulvestrant is subject to extensive and rapid distribution and is eliminated mainly by metabolism. The major route of excretion is via the feces with less than 1% being excreted in the urine. Fulvestrant has a high clearance, suggesting that it is a drug with high extraction ratio. The terminal half-life after intramuscular administration is governed by the absorption rate and was estimated to be 40-50 days.

Increased exposure to fulvestrant was observed in patients with moderate hepatic impairment (Child-Pugh class B). Fulvestrant has not been administered to patients with severe hepatic impairment (Child-Pugh class C) (FASLODEX® prescribing information). Therefore, patients with Child-Pugh class B and C will not be enrolled. No dose reductions for fulvestrant will be allowed in study CLEE011F2301.

1.2.3 Overview of ribociclib in combination with fulvestrant

Ribociclib and fulvestrant have the following toxicities in common: nausea, fatigue, vomiting, decreased appetite, constipation, dyspnea, cough, AST increase, headache, and back pain. These overlapping adverse events are expected to be tolerable and manageable.

In addition, there are no known drug interactions with fulvestrant. In vitro studies showed no relevant inhibition of the major CYP enzymes, including CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. The lack of inhibition of CYP3A4 was confirmed in an in vivo interaction study with midazolam. In addition, interaction studies with rifampicin (strong CYP3A4 inducer) and ketoconazole (strong CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics (FASLODEX® prescribing information). Therefore, a drug-drug interaction (DDI) involving fulvestrant and ribociclib is unlikely to occur.

The combination of ribociclib and fulvestrant is currently being explored in study [CLEE011X2108]. This is an open-label Phase Ib/II study in postmenopausal women with locally advanced or metastatic HR+/HER2- BC. The phase Ib dose escalation includes triple combination arms of ribociclib + BKM120 (pan-PI3K) + fulvestrant and ribociclib + BYL719(PI3K-alpha) + fulvestrant and a dose confirmation arm with ribociclib + fulvestrant.

As of 05-Jun-2015 , a total of 13 patients have been treated with the combination of ribociclib (600 mg daily on Day 1-21 of each 28-day cycle) and fulvestrant (500 mg every 28 days with 1 additional dose on Day 15 of Cycle 1) in study [CLEE011X2108]. Seven patients discontinued treatment, 1 adverse event was the reason for end of treatment and in the other 6 patient due to progressive disease. All patients have completed the first 28 days cycle. Of these 7 evaluable patients, there were no dose adjustments, interruptions or dose limiting toxicities. Grade 2/3 neutropenia was observed in 6 of the 7 patients. As of 04-Feb-2015, 5 patients are continuing to be treated with this combination, and 6 out of 7 patients have been exposed to the combination for more than 140 days. One patient met the dose limiting toxicity criteria wih a Grade 3 pulmonary embolism on Cycle 1. One patient discontinued after being hospitalized during Cycle 7 for Grade 4 atrial fibrillation, which was a serious adverse event and was suspected to be treatment related. Another patient discontinued at Cycle 5 due to progressive disease.

Table 1-2 contains the adverse events presented in more than 2 patients treated with the combination of ribociclib plus fulvestrant in [CLEE011X2108] and suspected to be study drug related.

Table 1-2 Adverse events suspected to be study drug related in [CLEE011X2108]

Table below is update with data including a cutoff incidence of more than 15%

Preferred term	All grades n (%)	Grade 3/4 n (%)
-Total	13 (100)	11 (84.6)
NEUTROPENIA	9 (69.2)	8 (61.5)
FATIGUE	9 (69.2)	2 (15.4)
NAUSEA	6 (46.2)	0
ANAEMIA	6 (46.2)	0
DECREASED APPETITE	5 (38.5)	0
WHITE BLOOD CELL COUNT	4 (30.8)	2 (15.4)
DIARRHOEA	4 (30.8)	0
VOMITING	3 (23.1)	0
THROMBOCYTOPENIA	3 (23.1)	0
ALANINE AMINOTRANSFERASE	2 (15.4)	1 (7.7)
ASPARTATE AMINOTRANSFERASE	2 (15.4)	1 (7.7)
PRURITUS	2 (15.4)	0
PLATELET COUNT DECREASED	3 (23.1)	0
DYSGEUSIA	2 (15.4)	0
ELECTROCARDIOGRAM QT	2 (15.4)	0
NEUTROPHIL COUNT DECREASED	2 (15.4)	2 (15.4)
BLOOD CREATININE INCREASED	2 (15.4)	0
LYMPHOCYTE COUNT DECREASED	2 (15.4)	0
ORAL PAIN	2 (15.4)	0

Preliminary results of ribociclib in combination with fulvestrant suggest that this combination is safe and tolerable. Preliminary PK analysis suggests that ribociclib (600 mg) and fulvestrant (500 mg) exposures were not affected in combination treatment. The best response for all 7 (100%) patients has been stable disease thus far.

Refer to the LEE011 (ribociclib) [Investigators Brochure] for more details.

2 Rationale

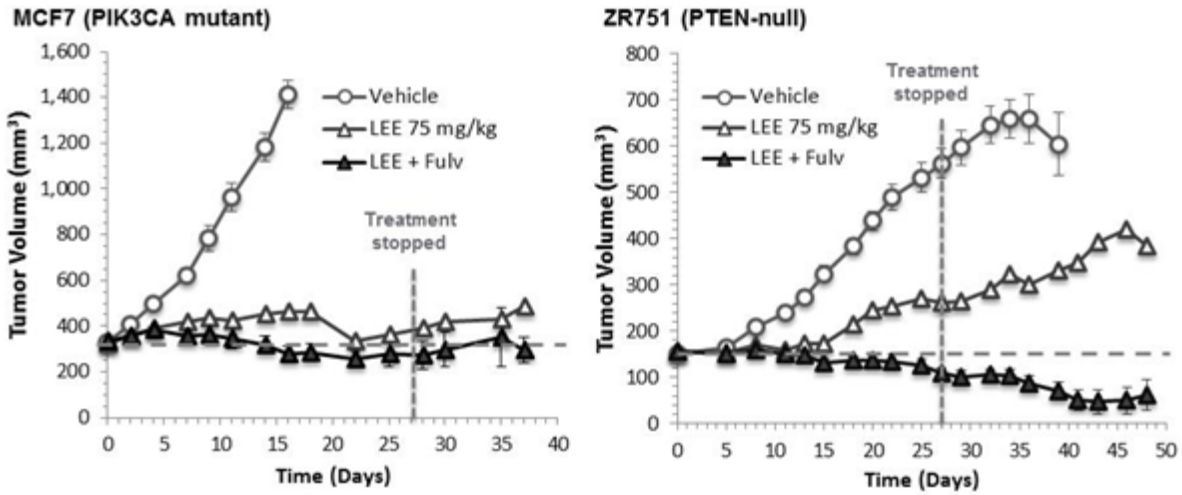
2.1 Study rationale and purpose

The rationale for combining ribociclib with fulvestrant is based on findings that a significant number of HR+, HER2-negative breast cancer patients are expected to have, or develop, resistance to endocrine therapies that have been given in the adjuvant or first line metastatic setting, and CDK4/6 pathway alterations appear to play a key role in the development of this 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). By targeting two distinct pathways (ER antagonism by fulvestrant, CDK4/6 pathway inhibition by ribociclib), it is hypothesized that this combination will result in prolonged progression free survival. Preclinically, improved responses have been shown with the addition of ribociclib to fulvestrant in various cell lines. Clinical experience has helped characterizing ribociclib safety profile and supported the initiation of phase III trials. A large number of patients have now been treated with ribociclib in phase I - III trials with an extensive number of patients having been exposed to doublet combination of ribociclib with endocrine therapy ([CLEE011X2107], [CLEE011X2108], [CLEE011X2106] [CLEE011A2301]).

Preclinical data (Novartis internal data, Figure 2-1), along with preliminary clinical safety and tolerability data from study [CLEE011X2108] (Section 1.2.3) for the combination of ribociclib and fulvestrant, support the conduct of this study.

Figure 2-1 Ribociclib plus fulvestrant in ER+ breast cancer xenograft models



The purpose of this study is to determine whether treatment with ribociclib plus fulvestrant will result in an improved clinical benefit compared to fulvestrant and placebo in men and postmenopausal women with HR+, HER2-negative advanced breast cancer who have received no or only one prior endocrine treatment for advanced disease.

2.2 Rationale for the study design

This is a randomized, placebo-controlled two-arm study with the objective to evaluate the efficacy and safety of adding ribociclib to fulvestrant in men and postmenopausal women with advanced breast cancer. The randomized, double-blind, placebo controlled, multicenter, parallel group design is the gold standard for phase III trials as it minimizes allocation bias, balancing both known and unknown prognostic factors in the assignment of treatments.

A randomization ratio (ribociclib+fulvestrant vs placebo+fulvestrant) of 2:1 is selected, since the efficacy and safety of fulvestrant is well characterized, a 2:1 randomization will allow a better evaluation of efficacy and safety of the ribociclib+fulvestrant combination. Randomization will be stratified by the following factors (see Section 4.1 for further details):

1. Lung or liver metastases (yes versus no)

2. Previous endocrine therapy

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

2.3 Rationale for dose and regimen selection

The ribociclib dose and regimen selected for this study is 600 mg daily 21 days on/7 days off. In the FIH study of single agent ribociclib in adult patients with solid tumors [CLEE011X2101], the MTD of ribociclib was 900 mg QD with a 3 weeks on/1 week off schedule. The recommended dose for future development was 600 mg QD with a 3 weeks on/1 week off schedule, which showed an acceptable safety profile, low risk for QTcF prolongation, adequate exposure, and preliminary evidence of disease stabilization as single agent. In the phase III study of ribociclib/placebo (600 mg) combined with letrozole (2.5 mg once daily) in postmenopausal women with advanced breast cancer HR+ HER-2 negative [CLEE011A2301], the most recent DMC took place on October 7, 2015 and reviewed safety of 664 patients , recommending to continue the study without changes.

Fulvestrant will be administered at the dose according to its approved label, 500 mg IM as two 250 mg 5 ml injections (one in each buttock) on days 1, 15, 29 and then monthly thereafter (FASLODEX® prescribing information).

Based on available data from preliminary results of patients treated with the combination of ribociclib at 600 mg and fulvestrant at 500 mg in study [CLEE011X2108], the combination is tolerable and a DDI between ribociclib and fulvestrant is unlikely. Therefore, these doses will also be used in this study.

2.4 Rationale for choice of combination drugs

Recent clinical data indicate that inhibitors of CDK4/6 are active in advanced ER+ breast cancer. Fulvestrant is acknowledged as an acceptable therapy in the first-line metastatic setting (Cruz Jurado 2011) and is approved after failure to prior antiestrogen therapy. In this study, we propose to use ribociclib, which directly targets pRb to interfere with the proliferation cycle, in combination with fulvestrant to prolong PFS in HR+, HER2-negative postmenopausal women with advanced breast cancer who have received no prior therapy or only one line of prior endocrine treatment for advanced disease.

The rationale to combine ribociclib with fulvestrant is based on the following:

- Preclinical data demonstrating additional benefit of the combination of CDK4/6 inhibition by ribociclib and estrogen pathway inhibition by fulvestrant compared to single agent activity (Section 2.1)
- The efficacy of fulvestrant in this patient population (Section 1.2.2)
- Preliminary safety findings of the combination of ribociclib and fulvestrant in study [CLEE011X2108]
- The low likelihood of a drug-drug interaction between ribociclib and fulvestrant and preliminary PK data from [CLEE011X2108] suggesting no changes in exposures.

2.5 Rationale for choice of comparator drugs

Patients enrolled in the study will either be in first line or in second line for the treatment of their metastatic disease.

In first line setting, currently approved treatment options include tamoxifen, AI or letrozole in combination with palbociclib (Section 1.1.2).

The recently presented data from the FIRST study, conducted in HR+ HER2-negative advanced breast cancer patients with no prior endocrine therapy or with long DFS after adjuvant endocrine therapy, showed superiority of fulvestrant 500 mg compared to anastrozole (Robertson 2014, Ellis 2015). Despite methodological limitations linked to indirect comparisons, the benefit brought by fulvestrant over anastrozole appears to be of the same extent than the one brought by the addition of palbociclib to letrozole -the results of both studies are being confirmed by phase 3 trials (Falcon and Paloma 2). Taken together, these data support fulvestrant 500 mg as an acceptable therapy in the first-line metastatic setting.

In second line setting, several acceptable options are available (NCCN 2.2015) and include Fulvestrant. In addition, Fulvestrant is currently approved for the treatment of HR+ MBC in postmenopausal women with disease progression following anti-estrogen therapy. Hence, fulvestrant is considered a standard therapy for patients who have progressed on or after treatment with other endocrine agents and who require a well-tolerated alternative therapy (Ciruelos 2014).

In conclusion, fulvestrant at the selected dose of 500 mg given intramuscularly at one month intervals, with an additional 500 mg dose given 2 weeks after the initial dose, is considered an appropriate comparator arm for this study.

2.6 Risks and benefits

2.6.1 Potential benefits to clinical trial participants

All patients enrolled in this trial will receive an active and valid endocrine therapy for first and second line treatment of men and post-menopausal women (see Section 2.5). They will be randomized to receive in addition ribociclib or placebo. Based on preclinical and preliminary clinical data (see Section 1.2.3), treatment with ribociclib in combination with fulvestrant is expected to be well tolerated and it is hypothesized that it will result in delayed disease progression by inhibiting proliferation of endocrine-resistant breast cancer cells.

2.6.2 Potential risks to clinical trial participants

Patients in this study will be carefully monitored for key toxicities that have been observed with ribociclib (see Section 1.2.1.2.1), fulvestrant (see Section 1.2.2) or the combination of both (see Section 1.2.3) with the following assessments (see Section 7): periodic laboratory, renal and liver function, urinalysis and ECG.

Risk will be further minimized by adherence to inclusion/exclusion selection criteria (see Section 5), avoidance of prohibited medication (see Section 6.6.3), close safety monitoring (see Section 8) and dose adjustment guidelines (see Section 6.5 and current fulvestrant prescribing information (FASLODEX® prescribing information). PK sampling will be

conducted in patients to assess plasma concentration of the study drug to evaluate any potential drug interaction. An independent data monitoring committee (IDMC) (see Section 8.6) will be constituted and will monitor safety, efficacy and available PK data as outlined in the protocol. A Steering Committee (SC) (see Section 8.7) will be established comprising of investigators and Novartis personnel participating in the trial to ensure transparent management of the trial according to the protocol. A Novartis Safety Management Team (SMT) periodically reviews and evaluates all emerging data across the ribociclib program for potential safety signal assessment in a timely manner.

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
To compare PFS between ribociclib in combination with fulvestrant to placebo in combination with fulvestrant among men and postmenopausal women with HR+, HER2-negative advanced breast cancer who received no or only one prior endocrine treatment for advanced disease	The primary end point is PFS based on local radiology assessments and using RECIST 1.1 criteria	
Secondary		Refer to Section 10.5
To compare the two treatment arms with respect to overall survival.	Overall survival	
To evaluate the two treatment arms with respect to overall response rate, clinical benefit rate, time to response and duration of response.	ORR and as defined by RECIST 1.1. CBR, defined as percentage of patients with CR, PR or SD lasting 24 weeks or longer, TOR, DOR per RECIST 1.1	
To evaluate the two treatment arms with respect to time to deterioration of ECOG performance status.	Time to definitive deterioration of ECOG performance status from baseline	
To evaluate the safety and tolerability of ribociclib in combination with fulvestrant.	Frequency/severity of AEs, laboratory abnormalities	
To evaluate patient reported outcomes for health-related quality of life in the two treatment arms.	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	
To characterize the pharmacokinetics (PK) of ribociclib (and relevant metabolites such as LEQ803) when given in combination with fulvestrant.	Concentration by time point for ribociclib (and relevant metabolites such as LEQ803)	

4 Study design

4.1 Description of study design

This is a randomized, phase III, double blind, placebo controlled, international study to determine the efficacy and safety of treatment with fulvestrant with ribociclib versus fulvestrant with placebo in men and postmenopausal women with HR+, HER2-negative advanced breast cancer. This study will consist of 4 phases: screening (up to 28 days), randomized treatment, post-treatment disease progression follow-up, and post-treatment survival follow-up.

Approximately 660 patients will be randomly assigned to one of the below treatment arms in a 2:1 ratio.

- Experimental arm (Arm A): **fulvestrant** (500 mg intramuscular [as two 5 mL injections] on Cycle 1 Days 1 and 15 (C1D1 and C1D15), and on CnD1 thereafter) + **ribociclib** (600 mg by mouth once daily for three weeks followed by one week break, in a 28-day cycle).
  OR
- Control arm (Arm B): **fulvestrant** (500 mg intramuscular [as two 5 mL injections] on Cycle 1 Days 1 and 15 (C1D1 and C1D15), and on CnD1 thereafter) + **placebo** (by mouth once daily for three weeks followed by one week break, in a 28-day cycle).

Randomization will be stratified by the following factors:

1. Lung or liver metastases: (yes versus no)
2. Previous endocrine therapy according to the below definition:

A) Patients treatment naïve for metastatic/advanced disease include:

i. Patients whose disease relapsed >12 months after completion of (neo)adjuvant endocrine therapy with no subsequent treatment for advanced/metastatic disease,

OR

ii. Patients with de novo advanced/metastatic disease (no prior exposure to endocrine therapy).

B) Patients who received up to 1 line of treatment for metastatic/advanced disease include:

i. Patients whose disease relapsed on or within 12 months from completion of (neo) adjuvant endocrine therapy, with no subsequent treatment for advanced/metastatic disease,

OR

ii. Patients whose disease relapsed > 12 months from completion of (neo) adjuvant endocrine therapy, and progressed on or after subsequent endocrine treatment for advanced/metastatic disease,

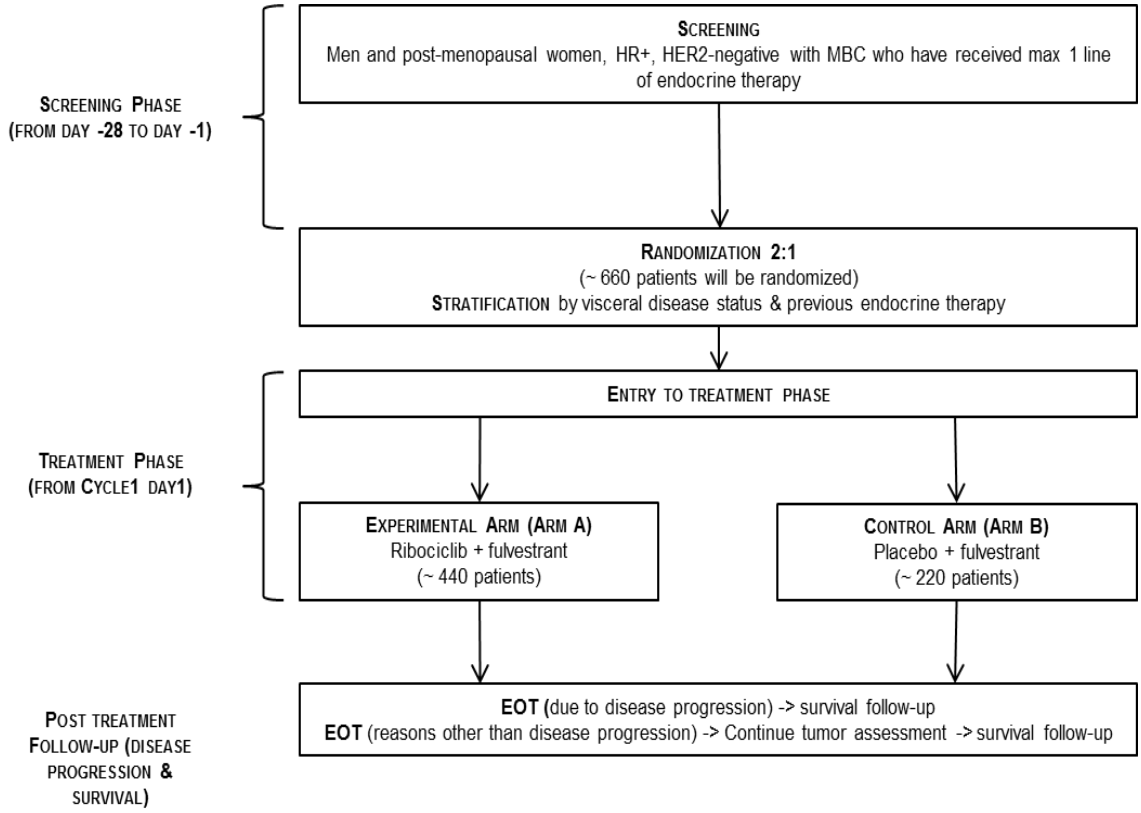
OR

iii. Patients with advanced/metastatic disease at the time of diagnosis that progressed on or after endocrine therapy for advanced/metastatic disease with no prior (neo) adjuvant treatment for early disease

Prior exposure to endocrine therapy subcategories included in groups A and B, were collated based on mPFS or TTP. Subcategory A grouped patients with PFS or TTP above 10 months (Paridaens et al. 2008; Mouridsen 2001; Robertson 2014; Finn 2015); whereas subcategory B grouped patients with shorter PFS or TTP around 4-6.5 months (Di Leo 2012; Dombernowsky 1998; Buzdar 1998; Johnston 2012).

Patients will be treated until disease progression, unacceptable toxicity, or discontinuation from the study treatment for any other reason (see Figure 4-1).PFS, as assessed by the local radiologists/investigators and using RECIST 1.1 criteria will be the primary endpoint. PFS as assessed through blinded independent central review will be used for supportive evidence of the primary efficacy endpoint.

Figure 4-1 Study Design



An Independent Data Monitoring Committee (IDMC) will be constituted and will monitor safety and efficacy as outlined in Section 8.6 and Section 10.7. A Steering Committee (SC) will be established comprised of investigators and Novartis personel participating in the trial to ensure transparent management of the study according to the protocol as outlined in Section 8.7.

If the study proceeds after a positive effect on PFS is declared (at final analysis of PFS), crossover to the experimental arm from the control arm is not permitted and investigators and patients will remain blinded to study treatment; all patients will continue to be followed for OS until the final OS analysis.

4.1.1 Screening phase

Men and postmenopausal women with HR+, HER2-negative advanced breast cancer will be screened for eligibility during the period up to 28 days immediately prior to starting the combination of fulvestrant + ribociclib or fulvestrant + placebo on study Day 1. During this time, the inclusion and exclusion criteria will be assessed and all screening assessments, laboratory tests, and procedures will be performed. Requested tumor tissue will be retrieved. Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to patient enrollment into the study in order to assure that all inclusion and exclusion criteria have been satisfied.

All study patients must be thoroughly informed about all aspects of the study, including the study agents, visit schedule, required evaluations, and all regulatory requirements for informed consent. The signed informed consent must be obtained to participate in this study prior to the performance of any study-related activities. If the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. Eligibility will be determined according to the inclusion/exclusion criteria as described in Section 5. A list of procedures to be performed at the time of screening is summarized in Table 7-1. Patients must meet all eligibility criteria to be considered for enrollment in the study.

4.1.2 Treatment phase

Patient eligibility will be checked once all screening procedures are completed. An eligibility review and confirmation will be embedded to the Interactive Response Technology (IRT) system. Please refer to and comply with detailed guidelines in the IRT manual. The IRT system will confirm the inclusion of eligible patients and randomize them in a 2:1 ratio to one of the two treatment groups described in Section 4.1.

Patients may continue study treatment until disease progression, occurrence of unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow-up, or the sponsor terminates the study. Patients will be followed for survival regardless of treatment discontinuation for any reason, and regardless of achieving the primary endpoint, until the planned number deaths for final OS analysis have been documented (except if consent is withdrawn or patient is lost to follow-up). An end of treatment visit will be performed when patients permanently discontinue study treatment.

All patients will have PK sampling; a subset (of approximately 150 patients) will have sparse PK collections on 3 occasions while the remainder will have a single trough PK sample on 3 occasions as detailed in Section 7.2.3.

4.1.3 Safety follow-up

After discontinuation of study treatment, all patients will be followed for safety, AEs and patient reported outcomes which will be collected until 30 days after last study therapy administration, except in case of death, loss to follow up or withdrawal of consent. For details please refer to Section 7.1.5.

4.1.4 Efficacy follow-up

Patients who discontinue treatment for reasons other than disease progression or withdrawal of consent for efficacy follow-up, will continue to be followed every 8 weeks ± 1 week for efficacy (i.e., tumor assessments and patient reported outcomes) during the first 18 months and every 12 weeks ± 1 week thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision. All scans will be acquired and analyzed for primary endpoint locally and will be sent to the CRO designated by Novartis for central imaging interpretation. If a patient starts a new anti-neoplastic treatment without withdrawing consent, the patient will continue to be followed for efficacy according to above specified protocol schedule until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision. For further details please refer to Table 7-1 and Section 7.1.6.

4.1.5 Survival follow-up

All patients will be followed for survival once they discontinue study treatment and tumor evaluations until the final number of OS events have been reached or the study is stopped for other reasons. Survival follow-up will be done every 12 weeks ± 1 week or earlier if a survival update is required to meet safety or regulatory needs. Survival information can be obtained by clinical visits or telephone calls (Section 7.1.7) until death, the patient is lost to follow-up, or the patient withdraws consent for survival follow-up.

[redacted]

4.2 Timing of interim analyses and design adaptations

There is no planned efficacy interim analysis for the primary PFS endpoint. Interim analysis of the secondary endpoint of OS will be performed if PFS is statistically significant. as detailed in Section 10.5.1 and Section 10.7.2.

4.3 Definition of end of the study

The end of the study for a given patient is defined as when the patient permanently discontinues study treatment with ribociclib + fulvestrant or placebo + fulvestrant and all the end of trial procedures are completed.

If the primary endpoint, PFS, is statistically significant at the final PFS analysis, data collection will continue during survival follow-up and End of Study will be declared after the final number of OS events are reached (or earlier if OS reaches statistical significance at the interim analysis for OS) and after all patients have discontinued study therapy and completed the safety follow-up period (until 30 days after treatment discontinuation).

If the primary endpoint, PFS, is not statistically significant at the final PFS analysis then End of Study will be declared after all patients have discontinued study therapy and completed the safety follow-up period (until 30 days after treatment discontinuation).

Patients continuing to derive benefit from study treatment at the end of the study in the opinion of the investigator will be able to continue receiving trial therapy on a separate protocol. Alternatively Novartis will provide study treatment to the investigator as per local regulations.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the assessments described in Section 7 for a discontinued or withdrawn patient should be performed. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The study will include men and postmenopausal women with HR+, HER2-negative advanced (loco regionally recurrent not amenable to curative therapy or metastatic) breast cancer who received no or only one line of prior endocrine treatment for advanced breast cancer.

Patients with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment will 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 treatment in the study.

The patients are not permitted to participate in any additional parallel investigational drug or device studies.

5.2 Inclusion criteria

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

Written informed consent must be obtained prior to any screening procedures.

1. [Retired from protocol version 0.0]

1a. Patient is an adult male/female ≥ 18 years old at the time of informed consent and has signed informed consent before any trial related activities and according to local guidelines.

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.

2. Female patients must be postmenopausal. Postmenopausal status is defined either by:
   - Prior surgical bilateral oophorectomy (with or without hysterectomy)
   - Age ≥60

- Age <60 and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal range per local normal range

Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status (NCCN 2.2015). Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression for the purpose of this trial.

3. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory (based on most recent analyzed biopsy).
4. Patient has HER2-negative breast cancer (based on most recent analyzed biopsy) 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.
5. Patient must have either:
   - Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1. (a lesion at a previously irradiated site may only be counted as a target lesion if there is a clear sign of progression since the irradiation).

     OR
   - If no measurable disease is present, then at least one predominantly lytic bone lesion must be present (patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation).
6. Patient has advanced (loco regionally recurrent not amenable to curative therapy (e.g. surgery and/or radiotherapy) or metastatic) breast cancer.

   Patients may be :
   - newly diagnosed advanced/ metastatic breast cancer, treatment naïve
   - relapsed with documented evidence of relapse more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced/metastatic disease
   - relapsed with documented evidence of relapse on or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced/metastatic disease
   - relapsed with documented evidence of relapse more than 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor) for advanced/metastatic disease
   - advanced/metastatic breast cancer at diagnosis that progressed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor)

Note: Patient who relapsed with documented evidence of relapse on/or within 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with

documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor) for metastatic/advanced disease will NOT be included in the study.

7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
8. [Retired from protocol version 0.0]

   8a. Patient has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory for eligibility):

   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
   - Platelets $\geq 100 \times 10^9$/L
   - Hemoglobin ≥ 9.0 g/dL
   - INR ≤ 1.5
   - Serum creatinine < 1.5 mg/dL
   - Total bilirubin < ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is $\leq 3.0 \times$ ULN or direct bilirubin $\leq 1.5 \times$ ULN.
   - 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
   - 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)

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 has received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant or any CDK4/6 inhibitor.
3. Patients has received prior neoadjuvant/adjuvant treatment with anthracyclines at cumulative doses of 450mg/m² or more for doxorubicin or 900 mg/m² or more for epirubicin.
4. Patient with a known hypersensitivity to any of the excipients of ribociclib or fulvestrant.
5. Patient with inflammatory breast cancer at screening.
6. Patient is concurrently using other anti-cancer therapy.
7. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects.
8. Patients with Child pugh score B or C.

9. Patient is currently receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.
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 received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia) and/or from whom ≥ 25% (Ellis 1961) of the bone marrow was irradiated.
12. Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell skin carcinoma or curatively resected cervical cancer.
13. 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.
14. 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).
15. Patient has a known history of HIV infection (testing not mandatory)
16. 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.)
17. [Retired from protocol version 0.0]

17a. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following:
    - History of angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG), myocardial infarction within 6 months prior to study entry
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - 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 medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by

safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug)
- Inability to determine the QTcF interval

- Clinically significant cardiac arrhythmias including but not limited to (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
- Systolic Blood Pressure (SBP) >160 mmHg or <90 mmHg
- Bradycardia (heart rate < 50 bpm at rest), by ECG (mean of triplicate) and pulse.
- Tachycardia (heart rate > 90 bpm at rest), by ECG (mean of triplicate) and pulse.
- On screening, inability to determine the QTcF interval on the ECG (ie: unreadable or not interpretable) or QTcF >450 msec (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs).

18. 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, pummelos, star-fruit, and Seville oranges.
    - Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
    - Herbal preparations/medications, dietary supplements (except vitamins).
19. 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).
20. Participation in a prior investigational study within 30 days prior to enrollment or within 5-half lives of the investigational product, whichever is longer.
21. Not able to understand and to comply with study instructions and requirements.

6 Treatment

6.1 Study treatment

For this study, the term "investigational drug" refers to Novartis study drug ribociclib. Fulvestrant is also being used in this study. Study treatment in this study refers to the combination of drugs in each of the study arms and includes ribociclib/placebo and fulvestrant.

Ribociclib will be supplied by Novartis or its designee as 200 mg hard gelatin capsules as individual patient supply packaged in bottles.

Fulvestrant will be procured locally according to local practice and regulation, or supplied by Novartis (or its designee). Storage conditions are described in the medication label. Medication labels will comply with the legal requirements of each country and be printed in the local language.

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

6.1.1 Dosing regimen

All eligible patients will be randomized starting from Cycle 1 Day 1 to receive either:

- Fulvestrant + ribociclib
- Fulvestrant + placebo

Ribociclib or placebo will be given orally once daily on days 1-21 of each 28 day cycle. Days 22-28 will be a "rest" period from dosing with ribociclib or placebo.

Fulvestrant will be administered intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on Cycle 1 Day 1 (C1D1), Cycle 1 Day 15 (C1D15), Cycle 2 Day 1 (C2D1) and every 28 days thereafter (i.e., the first day of each 28 day cycle) as per the (FASLODEX® prescribing information). There will be no "rest" in the fulvestrant schedule.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
fulvestrant	Two 5ml injections for i.m. administration	500 mg	Dosed every 28 days (Cycle n Day 1) with 1 additional dose on Day 15 of Cycle 1
ribociclib/placebo	Capsule for oral use	600 mg	Once daily; days 1 to 21 in a 28-day Cycle

The study drugs will be administered as a flat-fixed dose and not by body weight or body surface area. There shall be no breaks between dosing cycles. A complete cycle of treatment is defined as 28 days. All study treatment drugs should be administered as described below in Section 6.1.1.1 and Section 6.1.1.2.

The investigator or responsible site personnel will instruct the patient to take the study drugs as per protocol (promote compliance). Patients will be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel will ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed.

6.1.1.1 General dosing guidelines

The study treatments should be taken as follows:

- On scheduled visit days, patients must take study treatments in the clinic under the supervision of the Investigator or designee. On all other days patients will take ribociclib/placebo at home.
- Patients should be instructed to take the study treatment of ribociclib/placebo capsules together with a large glass of water (~250 mL or ~8 oz) once a day at the same time each day. For the first cycle, patients must take ribociclib/placebo in the morning due to PK assessments. Once the PK assessments have been completed, patients can determine if they prefer am or early afternoon dosing but should maintain a consistent time regardless of am or early afternoon dosing. Evening doses are strongly **not recommended**.

- In general, study treatment may be taken without regard to meals. Please see Section 6.1.1.2 below for additional guidelines for fasting lab assessments and for sparse PK collection.
- Patients will be instructed to swallow the capsules whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably for an additional 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
- No herbal or dietary supplements are permitted.
- Multivitamins are permitted.

6.1.1.2 Additional guidelines for fasting lab assessments and sparse PK

Fasting considerations for lab assessments (e.g. glucose and lipid profile)

- The patient should be fasting overnight (i.e., at least 8-12 hours prior to the blood collection) for all visits with fasting glucose, lipid profile sampling and [redacted]
- Water is allowed during all fasting periods; however coffee, tea and juice are not permitted during the fasting period.

Meal considerations for sparse PK collection

- Only for the sparse PK group, the meal condition (fasting, low fat, high fat) must be recorded on the eCRF **within ± 30 minutes of the dose** on C1D15 and C2D15. The meal condition is an estimate; however guidance is provided below.
- On C1D15 and C2D15, when PK is paired with ECG assessments, patients may consume breakfast only after fasted pre-dose blood samples (fasting glucose, fasting lipid profile) have been collected.
- Pre-dose PK should be collected approximately 24 hrs after the last dose (± 2 hrs) and immediately before the next dose.
- A high-fat meal typically contains 800-1000 calories with approximately 50% of the calories coming from fat (500-600 calories) (FDA Guidance for Industry for Food-effect Bioavailability and Fed Bioequivalence Studies, December 2002). An example of a high-fat meal could be two eggs, 2 slices of bread, 1 tablespon butter, 1 tablespoon jelly, 3 strips of bacon, 4 ounces of hash brown potato, and 8 ounces of whole milk. A low-fat meal could be approximately 300-500 calories with approximately 25% of the calories coming from fat (75-125 calories) and could include 2 slices of bread, 1 tablespoon light

fat margarine, 1 tablespoon jelly, and 8 ounces of skim milk (USDA National Nutrient Database for Standard Reference, 2010).

6.1.1.3 Fulvestrant dosing

Fulvestrant 500 mg will be given after randomization at Cycle 1 Day 1, at Cycle 1 Day 15 (with a ± 3 day window) and then at Day 1 of each subsequent cycle during the randomized treatment phase (with ± 3 day window). Fulvestrant is administered intramuscularly into the buttocks slowly as two 5mL injections, one in each buttock. No dose modification of fulvestrant is planned in this study.

For information on fulvestrant and management of related adverse events, refer to the FASLODEX® SmPC or local Prescribing Information.

6.1.2 Guidelines for continuation of treatment

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

Patients who permanently discontinue fulvestrant for any reason must discontinue ribociclib/placebo, and move to End of Treatment phase, but will remain on study for follow-up evaluations (i.e. tumor follow-up and patient reported outcomes). Patients who permanently discontinue ribociclib/placebo may continue on the study on fulvestrant per investigator's discretion and will continue to be followed for safety and/or efficacy.

6.1.3 Ancillary treatments

Not applicable.

6.1.4 Rescue medication

Not applicable.

6.1.5 Treatment duration

Patients will be treated until disease progression (radiologically documented according to RECIST 1.1) or until discontinuation of study treatment due to any other reason (see Section 7.1.5).

6.2 Dose escalation guidelines

Not applicable

6.3 Patient numbering, treatment assignment or randomization

6.3.1 Patient numbering

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

entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface at that location.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient was not randomized.

6.3.2 Treatment assignment or randomization

Patients will be randomized to one of the **two** treatment arms (Section 4.1 and Section 6.1) in a ratio of 2:1.

Randomization will be stratified by the following factors:

1. Lung or liver metastases: (yes versus no)
2. Previous endocrine therapy

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

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.3.3 Treatment blinding

This is a double blind study. In particular, patients, investigators, study team, or anyone involved in the study conduct will remain blinded to the identity of the treatment from the time of randomization until database lock. The local (or Novartis-designated) radiologists will remain blinded to the identity of the treatment from the time of randomization until final database lock.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible to anyone involved in the conduct of the study. The identity of the treatments will be concealed by the use of investigational drugs (ribociclib or ribociclib matching placebo)

that are identical in packaging, labeling, schedule of administration and in appearance. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients.

Unblinding of study drug assignment will only occur in the case of patient emergencies (Section 8.3), for regulatory reporting purposes and at the conclusion of the study.

In rare cases when unblinding occurs because of emergency patient management, the actual treatment arm will not be communicated to any of the Novartis employees involved in running the trial in order to remain blinded.

An independent statistical group (external to Novartis), not involved in the trial conduct, will prepare data reports for the DMC. An independent clinical pharmacologist will analyze the data from patients with PK sampling if the data were to be presented at the DMC meetings. Details will be presented in the DMC charter.

6.4 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/placebo on an outpatient basis. The investigator shall provide the patient with instructions for ribociclib/placebo administration according to the protocol.

Fulvestrant should be dispensed according to local prescribing information and practice.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study treatment as per protocol. Study treatment 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.

6.4.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a [specific visit or dose/dose level]. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

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

Table 6-2 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
ribociclib or placebo	Capsules in bottles	Labeled as 'LEE011/placebo' Study treatment packaging has a 2-part

Study treatments	Packaging	Labeling (and dosing frequency)
		label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment arms.
fulvestrant	Refer to local product information	Refer to local product information

6.4.2 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.

Study treatments will be procured locally according to local practice and regulation, or supplied by Novartis (or its designee).

6.4.3 Study drug compliance and accountability

6.4.3.1 Study drug compliance

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

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of ribociclib in plasma.

6.4.3.2 Study drug accountability

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

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

6.4.3.3 Handling of other study treatment

Not applicable.

6.4.4 Disposal and destruction

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

6.5 Dose modifications

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

6.5.1.1 Fulvestrant

The established clinical dose of fulvestrant (500 mg) will be used in each arm and no dose modification of fulvestrant is planned in this study (Table 6-3). For information on fulvestrant and management of related adverse events, refer to the FASLODEX® SmPC or local Prescribing Information.

6.5.1.2 Ribociclib/placebo

Recommendations for dose reduction, interruption or discontinuation of ribociclib in the management of study drug related adverse reactions are summarized in Table 6-4, Table 6-5, Table 6-6 and Table 6-7. No dose modification for fulvestrant is permitted.

Table 6-3 Dose modification guidelines

	Ribociclib/placebo (3 weeks on/1 week off schedule)		Fulvestrant	
	Dose	Number of capsules & strength	Dose	Number of injections & strength
Starting dose	600 mg	3 x 200 mg capsules	500 mg	2 x 250mg (5 mL) injections
First dose reduction	400 mg	2 x 200 mg capsules	No dose modification allowed	
Second dose reduction	200 mg	1 x 200 mg capsules	No dose modification allowed	

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 6-4, Table 6-5, Table 6-6 and Table 6-7 or listed in Section 7.1.3, treatment must be discontinued.

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

The results of the local laboratory will be recorded in the eCRF if any of the following criteria are met:

- A treatment decision was made based on the local results, or
- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event severity is worse than the one reported by the central lab, or
- There are no concomitant central results available

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used.

Table 6-4 The results of the local laboratory will be recorded in the eCRF if any of the following criteria are met:

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/placebo 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/placebo at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib/placebo to the next lower dose level.
Grade 4(<25 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib/placebo at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib/placebo.
Absolute neutrophil count (ANC)	
Grade 1 (≥1.5 x 10^9/L)	No dose adjustment required.
Grade 2 (≥1.0 - <1.5 x 10^9/L)	No dose adjustment required.
Grade 3 (≥0.5 - <1.0 x 10^9/L)	Dose interruption until recovery to ≥1.0 x 10^9/L. Re-initiate ribociclib/placebo 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/placebo dose to the next lower dose level.
Grade 4 (<0.5 x 10^9/L)	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate ribociclib/placebo 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/placebo 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/placebo.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib/placebo.
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/placebo at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib/placebo.

Table 6-5 Ribociclib/placebo dose adjustment and management recommendation for hepatic toxicities

Please refer to Section 6.5.1.2.1 for additional information.

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/placebo 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/placebo
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of ribociclib/placebo If resolved to ≤ grade 1 in ≤ 21 days, lower 1 dose level of ribociclib/placebo 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 /placebo
Grade 4 (> 10.0 x ULN)	Discontinue ribociclib/placebo
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/placebo 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/placebo
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of ribociclib/placebo until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib/placebo Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption

	If recovery to ≤ baseline grade is > 28 days, discontinue ribociclib/placebo If toxicity recurs, discontinue ribociclib/placebo
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/placebo 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./placebo
Grade 4 (> 20.0 x ULN)	Discontinue ribociclib/placebo
AST or ALT and concurrent Bilirubin	
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT > 3 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/placebo
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.	

6.5.1.2.1 Additional follow-up for hepatic toxicities

Increase in transaminases combined with total bilirubin (TBIL) increase may be indicative of drug-induced liver injury (DILI), and should be considered as clinically important events. The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 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, 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**. After dose resumption repeat liver enzyme and bilirubin tests twice weekly during the first 2 weeks, afterwards the 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.
- Obtaining a PK sample, as close as possible to last dose of study drug
- Obtaining a 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.

6.5.1.3 Additional follow-up for QTcF prolongation

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

Grade	Dose Modification
For All Grades	• Check the quality of the ECG and the QT value and repeat if needed. • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If below the lower limit of normal, interrupt ribociclib/placebo administration, correct with supplements as soon as possible, and repeat electrolytes until documented as normal. • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. • Check compliance with correct dose and administration of ribociclib/placebo. • Consider collecting a time matched PK sample; record date and time of last study drug intake.
1* QTcF 450-480 ms	No dose adjustment required.
2* QTcF 481-500 ms	Interrupt ribociclib/placebo. Perform a repeat ECG one hour after the first QTcF of ≥ 481 ms. If QTcF , 481 ms, restart ribociclib/placebo at the same dose. No dose adjustment required for first occurrence. If QTcF remains ≥ 481 ms, repeat ECG as clinically indicated until the QTcF returns to < 481 ms. Restart ribociclib/placebo at the same dose. No dose adjustment required for first occurrence. If QTcF ≥ 481 ms recurs, ribociclib/placebo should be reduced by 1 dose level. Refer to Table 6-1 for dosing schedule. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had study treatment interrupted due to QTcF ≥ 481 ms
3 QTcF ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib/placebo. Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. Perform a repeat ECG one hour after the first QTcF of ≥ 501 ms. If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as clinically indicated until the QTcF returns to < 481 ms. If QTcF returns to < 481 ms, ribociclib/placebo will be reduced by 1 dose level. Refer to Table 6-1 for dosing schedule. 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/placebo
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/placebo. • Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.
	*All values refer to the average of triplicate measurements

6.5.1.3.1 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 below the lower limit of normal, interrupt ribociclib/placebo administration, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

Patients who experience non-acute renal impairment of grade 2 or higher during the treatment period should discontinue ribociclib/ placebo treatment and should be followed for safety assessments.

Table 6-7 Ribociclib/placebo 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/placebo at the same dose. If the same toxicity recurs at grade 2, interrupt ribociclib/placebo until recovery to grade ≤1. Re-initiate ribociclib/placebo at the next lower dose level.
3	Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib/placebo at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce ribociclib/placebo dose the next lower dose level. If toxicity recurs at grade 3, discontinue ribociclib/placebo.
4	Discontinue ribociclib/placebo and treat with appropriate medical therapy.

6.5.1.3.2 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. Based on rat ADME data, ribociclib was predominantly excreted in the in the bile as metabolites, with limited excretion of unchanged drug in urine. A human ADME study is ongoing to confirm the metabolic and excretion pathways of ribociclib in humans.

For fulvestrant, no dose adjustments are recommended for patients with mild to moderate renal impairment (creatinine clearance ≥30 ml/min). Safety and efficacy for fulvestrant have not been evaluated in patients with severe renal impairment (creatinine clearance <30 ml/min), and, therefore, caution is recommended in these patients (FASLODEX® prescribing information).

Hepatic Impairment

Ribociclib has not been investigated in patients with hepatic impairment.

For fulvestrant, increased exposure to fulvestrant was observed in patients with moderate hepatic impairment (Child-Pugh class B). Fulvestrant has not been administered to patients with severe hepatic impairment (Child-Pugh class C) (FASLODEX® prescribing information). Therefore, patients with Child-Pugh class B and C will not be enrolled. No dose reductions

for fulvestrant will be allowed in study CLEE011F2301 therefore patients with baseline hepatic impairment are excluded from the study.

Elderly

Physicians should exercise caution in monitoring the effects of ribociclib in the elderly. Insufficient data are available to provide a dosage recommendation.

6.5.2 Follow-up for toxicities

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

6.5.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping recommendations are included in this protocol. Refer to Section 6.5 for details.

6.6 Concomitant medications

6.6.1 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 treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

6.6.1.1 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.
- If bisphosphonate/denosumab therapy is to be started after the first dose of study drug, prior consultation and approval by Novartis is required and the reason for its use must be clearly documented.

Patients taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The days of PK blood sampling should be representative of the other study days with regard to the use of the

chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of PK sampling, if medically feasible.

6.6.1.2 Hematopoietic growth factors

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

6.6.1.3 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 (see Appendix 3).

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 LEE011 (ribociclib) [Investigator's Brochure] and fulvestrant package insert for information on possible interactions with other drugs.

6.6.2 Concomitant therapy requiring caution

Medications to be used with caution during combined ribociclib/placebo and fulvestrant treatment in this study are listed below (see Table 14-2 in Appendix 1, this list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions). These medications should be excluded from patient use if possible. If they must be given based on the investigator's judgment, then use with caution and consider a ribociclib/placebo 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
- Strong inhibitors of BSEP
- Medications that carry a possible risk for QT prolongation
- Sensitive substrates of the renal transporters, MATE1 and OCT2
- Sensitive substrates of BCRP
- Immunosupressive therapies

6.6.2.1 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby 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)

6.6.3 Prohibited concomitant therapy

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

- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with a narrow therapeutic index
- Medications with a known risk for QT prolongation
- Other investigational and antineoplastic therapies

In addition, the use of herbal preparations/medications and dietary supplements (except for vitamins) are prohibited throughout the study, as a potential drug-drug interaction is possible. Herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

6.6.4 Drugs with QT prolongation

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.

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

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

The following CRF(s) will be used as source document(s): local lab results.

Allowed visit windows are specified as follows:

- Screening assessments, apart from those listed below, must occur within 28 days of the randomization as per Table 7-1.
- Vital signs, physical exam, ECOG performance status, required labs, physical exam should be performed within 7 days of randomization.

Note: If the physical examination was performed ≤ 7 days prior to the first dose of ribociclib/placebo, then they do not need to be repeated on Cycle 1 Day 1.

- In order for an accurate evaluation of baseline QTc, a total of three 12-lead ECGs will be performed at screening between -7 and -1 day.
- Randomization and Cycle 1 Day 1 should preferably occur on the same day. A maximum of a 3 days window between randomization and Cycle 1 Day 1 visit is permitted.
- For all visits (including PK visits C1D15, C2D1 and C2D15), a general ±3 days visit window is permitted on assessments to take into account scheduling over public holidays, if not explicitly specified otherwise.
- For PK sampling, the samples may be obtained within the time window specified in Table 7-6 and Table 7-7.
- Radiological and patient reported outcome assessments must be performed as outlined in Table 7-1. A visit window of ± 7 days is allowed. (The whole body bone scan should be performed within 42 days or 6 weeks prior to randomization).
- Any screening assessments required within -7 to -1 days must be repeated if Cycle 1 Day 1 visit is delayed more than 7 days after randomization visit.Every effort should be made to follow the schedule outlined in Table 7-1.

Table 7-1 Visit evaluation schedule

	Category	Reference to protocol section	Screening phase		Treatment phase							Post treatment follow-up phase			[redacted] and Survival phase
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3**	**Subsequent cycles**	**End of study treatment (EOT)**	**Safety follow-up**	**Efficacy follow-up**	**End of post-treatment follow-up**	**Survival follow-up**
Study days			**-28 to -1**	**-7 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose**	**Last dose + 30 days**	**Every 8 weeks (if applicable)**		**Every 12 weeks**
Screening															
Study Informed Consent	D	7.1.1	x												
IRT Screening (after ICF signature)	S	7.1.1	x												
Disposition Assessment															
End of Phase Disposition	D			x							x			x	
Patient history															
Demography	D	7.1.1.3	x												
Inclusion/exclusion criteria	D	7.1.1.3		x											
Medical history and current medical conditions	D	7.1.1.3	x												
ER and PgR status	D	7.1.1.3	x												
HER2 status	D	7.1.1.3	x												

	Category	Reference to protocol section	Screening phase		Treatment phase							Post treatment follow-up phase			[redacted] and Survival phase
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3**	**Subsequent cycles**	**End of study treatment (EOT)**	**Safety follow-up**	**Efficacy follow-up**	**End of post-treatment follow-up**	**Survival follow-up**
Study days			**-28 to -1**	**-7 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose**	**Last dose + 30 days**	**Every 8 weeks (if applicable)**		**Every 12 weeks**
Diagnosis and extent of cancer	D	7.1.1.3	x												
Prior antineoplastic therapy	D	7.1.1.3	x												
Prior / concomitant medications	D	7.1.1.3	Continuous – up to 30 days after last dose												
Randomization															
Eligibility checklist (within IRT)	S	7.1.1			x										
IRT - Randomization	D	7.1.1			x										
IRT - study drug administration	S	7.1.1			x		x		x	x	x				
Physical examination															
Physical examination	S	7.2.2.1		x			x		x	x	x				
Performance status	D	7.2.2.4		x	x		x		x	x	x				
Height	D	7.2.2.3	x												
Weight	D	7.2.2.3	x		x		x		x	x	x				
Vital signs	D	7.2.2.2		x	x	x	x		x	x	x				
Laboratory assessments															

	Category	Reference to protocol section	Screening phase		Treatment phase							Post treatment follow-up phase			[redacted] and Survival phase
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3**	**Subsequent cycles**	**End of study treatment (EOT)**	**Safety follow-up**	**Efficacy follow-up**	**End of post-treatment follow-up**	**Survival follow-up**
Study days			**-28 to -1**	**-7 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose**	**Last dose + 30 days**	**Every 8 weeks (if applicable)**		**Every 12 weeks**
Hematology	D	7.2.2.5.1		x		x	x		x	x	x				
Chemistry with fasting glucose	D	7.2.2.5.2		x		x	x		x	x	x				
Fasting Lipid Panel	D	7.2.2.5.3		x					x	Every 3rd cycle	x				
Coagulation	D	7.2.2.5.4		x		As clinically indicated					x				
Urinalysis	D	7.2.2.5.5		x			x		x	x	x				
[redacted]															
Tumor assessment															
Tumor evaluation (RECIST 1.1)	D	7.2.1	x		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, and at EOT (If PR/CR is reported, confirmation of response is required; confirmatory assessment should be performed ≥ 4 weeks after response is first documented)										

	Category	Reference to protocol section	Screening phase		Treatment phase							Post treatment follow-up phase			[redacted] and Survival phase
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3**	**Subsequent cycles**	**End of study treatment (EOT)**	**Safety follow-up**	**Efficacy follow-up**	**End of post-treatment follow-up**	**Survival follow-up**
Study days			**-28 to -1**	**-7 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose**	**Last dose + 30 days**	**Every 8 weeks (if applicable)**		**Every 12 weeks**
Fluid/Tissue collection results (if available)	D	7.2.1	As clinically indicated until disease progression												
Whole body bone scan	D	7.2.1	x (within 42 days prior to randomization)		As clinically indicated										
Cardiac assessment															
Triplicate ECG (standard 12-lead)	D	7.2.2.6.1		x		x	x	x	x	x For all cycles up to Cycle 6	x				
					As clinically indicated										
ECHO or MUGA with EF	D	7.2.2.6.2	x		As clinically indicated										

	Category	Reference to protocol section	Screening phase		Treatment phase							Post treatment follow-up phase			[redacted] and Survival phase
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3**	**Subsequent cycles**	**End of study treatment (EOT)**	**Safety follow-up**	**Efficacy follow-up**	**End of post-treatment follow-up**	**Survival follow-up**
Study days			**-28 to -1**	**-7 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose**	**Last dose + 30 days**	**Every 8 weeks (if applicable)**		**Every 12 weeks**
Safety															
Adverse events	D	8.1	Continuous – up to 30 days after last dose												
Pharmacokinetics															
Sparse PK	D	7.2.3				x	x	x							
Meal record (high fat/low fat/fasting for sparse PK)	D	6.1.1.2				x		x							
Trough PK	D	7.2.3				x	x	x							
[redacted]															

	Category	Reference to protocol section	Screening phase		Treatment phase							Post treatment follow-up phase			[redacted] and Survival phase
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3**	**Subsequent cycles**	**End of study treatment (EOT)**	**Safety follow-up**	**Efficacy follow-up**	**End of post-treatment follow-up**	**Survival follow-up**
Study days			**-28 to -1**	**-7 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose**	**Last dose + 30 days**	**Every 8 weeks (if applicable)**		**Every 12 weeks**
[redacted]															
Patient Quality of life questionnaires															
EORTC QLQ-C30	D	7.2.6.1	x		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, and at EOT										
EQ-5D-5L	D	7.2.6.2	x		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, and at EOT										
BPI-SF	D	7.2.6.3	x		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, and at EOT										
[redacted]															
Study Drug administration															
fulvestrant	D				x	x	x		x	x					

	Category	Reference to protocol section	Screening phase		Treatment phase							Post treatment follow-up phase			[redacted] and Survival phase
Visit name			**Screening**		**Cycle 1**		**Cycle 2**		**Cycle 3**	**Subsequent cycles**	**End of study treatment (EOT)**	**Safety follow-up**	**Efficacy follow-up**	**End of post-treatment follow-up**	**Survival follow-up**
Study days			**-28 to -1**	**-7 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose**	**Last dose + 30 days**	**Every 8 weeks (if applicable)**		**Every 12 weeks**
ribociclib (LEE011) / placebo	D				Day 1 to Day 21 daily, Day 22 to Day 28 off										
Discontinuation															
IRT – Discontinuation	S	7.1.3									x				
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6									x	x	X		x
Survival follow-up	D	7.1.7													x

7.1.1 Screening

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

Note: Any screening assessment that is done outside the screening window (Day -28 to Day -1 or Day -7 to Day -1 as applicable) must be repeated prior to randomization.

Re-screening of patients is only allowed once per patient if the patient was not registered as entering the treatment phase before (i.e. IRT randomization). In this case the Subject No. assigned to the patient initially will be used and the patient will be identified with this number throughout her entire participation to the study.

Any screening assessments required within -7 to -1 days must be repeated if Cycle 1 Day 1 visit is delayed more than 7 days after randomization visit.For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria. A new informed consent form must be signed only if there is an interruption in the patient's eligibility evaluation and the investigator chooses to re-screen the patient following screen failure; the 28 day screen period does not apply to the informed consent process. If a new informed consent form is signed, adverse events and medical history will be assessed relative to the new informed consent date.

Assessments of patient reported outcomes should be collected prior to any clinical assessments, drug dosing or diagnostic testing.

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

7.1.1.1 Eligibility screening

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

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8.2 for SAE reporting details).

7.1.1.3 Patient demographics and other baseline characteristics

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

- Demography (Date of birth and initials (where permitted), sex, race, ethnicity, source of patient referral)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade.
- ER, PgR and HER2 status
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.
- Patient-reported outcome questionnaires (EORTC QLQ-C30, EQ-5D-5L, and BPI-SF (See Section 7.2.6).

Furthermore the following assessments will be performed:

- Vital signs
- Height, weight
- Physical examination
- Performance status (ECOG)
- Laboratory evaluations (hematology, PT, INR, chemistry, lipid panel, urinalysis)
- ECG
- ECHO/MUGA
- Radiological assessments (e.g. CT Scan)

7.1.2 Treatment period

Patients will be treated with fulvestrant + ribociclib or fulvestrant + placebo until disease progression, unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow up, death, discontinuation from the study treatment due to any other reason or the sponsor terminates the study. For details of assessments, refer to Table 7-1.

7.1.3 Discontinuation of Study Treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every reasonable effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages.

They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

Patient may be withdrawn from the study treatment under the following circumstances:

Emergence of adverse events where the recommendation as per Section 6.5.1.2 is discontinuation of ribociclib therapy (including, but not limited to QTcF ≥ 501 msec, confirmed at repeated ECG measurements and recurrent after dose adjustment was performed; documented episode of ventricular tachycardia, or ventricular fibrillation; complete heart block (Grade III AV block) or Second degree AV block Mobitz type II as well as any relevant hepatotoxicity events).

- Lost to follow up
- Physician decision
- Progression of disease
- Study terminated by the sponsor
- Protocol deviation
- Technical problems.

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

- Pregnancy
- Death
- Subject/guardian decision

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

- Adjustments to study treatment that result in discontinuation. Please refer to Section 6.5
- Use of prohibited medication. Please refer to Section 6.6.3

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.1.5 and Section 7.1.6. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7. 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 End of Post Treatment Phase Disposition CRF page.

Patients who discontinue study treatment should be scheduled for an End of Treatment (EOT) visit within 15 days following the date study treatment is permanently discontinued, at which time all of the assessments listed for the EOT visit will be performed. For details of

assessments, refer to Table 7-1. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

An End of phase disposition eCRF page should be completed, giving the date and reason for stopping the study treatment. If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the EOT eCRF page. The EOT visit is not considered the end of the study.

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

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.1.3.1 Replacement policy

Not applicable.

7.1.4 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

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

7.1.5 Follow up for Safety Evaluations

All patients will be followed up for safety up to 30 days after last dose of study treatment (fulvestrant + ribociclib/placebo). Patients whose treatment is interrupted or discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first. This could include all study assessments appropriate to monitor the event.

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

7.1.6 Efficacy follow-up

For patients who discontinue treatment for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments (see Section 7.2.1.1) and patient reported outcomes (see Section 7.2.6) must continue to be performed every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, lost to follow-up, or any other reasons listed in Section 7.1.9. At that time, the reason for study completion should be recorded on the End of Post treatment phase Disposition eCRF page. If a patient starts a new anti-cancer therapy prior to progression, tumor evaluations should continue with the same above schedule (Table 7-1) until disease progression is documented.

7.1.7 Survival follow-up

All patients will be followed for survival status every 12 weeks (see Section 4.1.5) regardless of start of new antineoplastic therapy or any other treatment discontinuation reason, until death, lost to follow-up, or withdrawal of consent. Additional survival assessments may be performed outside the 12 weeks follow up schedules if a survival update 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.

[redacted]

7.1.8 Lost to follow-up

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

7.1.9 End of post-treatment follow-up

Prior to collecting survival follow-up information, the end of post treatment phase disposition eCRF page will be completed once a patient has discontinued study treatment, completed safety follow-up, and can no longer perform efficacy assessment.

End of post-treatment follow-up may occur one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Progressive disease

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

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Imaging tumor assessments

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.1 (Appendix 2) based on RECIST Version 1.1 (Eisenhauer et al 2009). Further details regarding blinded independent review committee (BIRC) assessment will be provided in the BIRC charter. The central review of the scans will be carried out in a blinded fashion. The decision regarding patient management will remain with the local investigator.

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

Imaging assessments will be performed at screening within 28 days prior to randomization and subsequently every 8 weeks following randomization, using the randomization date as the reference date (not the date of the previous tumor assessment), during the first 18 months and every 12 weeks thereafter. See Table 7-2 for details of assessments. The 8-week (or 12 week) interval should be respected regardless of whether study treatment is temporarily withheld or unscheduled assessments performed.

After baseline, all assessments should be performed within ±7 days of the scheduled day of assessment. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up.

If a patient discontinues treatment for reasons other than radiological documentation of progression of disease, an efficacy assessment should be performed at the time of End of Treatment unless a CT/MRI for tumor measurement was performed within 21 days. Efficacy assessments should continue as per the scheduled visit per Table 7-1 and Table 7-2.

To the extent possible, each lesion should be assessed using the same imaging method throughout the study.

All patients will undergo CT or MRI of the chest, abdomen and pelvis at baseline and subsequent scheduled visits per Table 7-1 and Table 7-2. The preferred imaging methodology is CT with intravenous (i.v.) contrast. However, if at baseline, a patient is known to have a contraindication to CT i.v. contrast media or develops a contraindication during the trial, a non-contrast CT of chest (MRI is not recommended due to respiratory artifacts) plus contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

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

Color photography, including a metric ruler to estimate the size of the lesion, must be acquired for all **skin lesions** present at baseline per instructions provided in the manual from the designated vendor. These should be followed throughout the study according to the schedule outlined in Table 7-2.

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

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

Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments performed not less than 4 weeks and after the criteria for objective response are first met. In case tumor assessment is performed <8 weeks from the first assessment of an objective response to confirm PR/CR, subsequent tumor assessments should revert back to the protocol schedule outlined in Table 7-1.

Positron Emission Tomography (PET)/CT may be used only if the CT component is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 2).

If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Any lesions in previously irradiated areas should not be considered measurable unless they have experienced progression since the radiotherapy. Any pre-existing radiographic findings which may mimic metastatic disease and any prior radiotherapy should be recorded in the eCRF.

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

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

All study imaging performed, including any intercurrent or off-schedule imaging studies acquired (e.g., to fulfill a progression or response criterion), should be submitted to the designated imaging CRO for quality control promptly after acquisition. If an off-schedule imaging assessment is performed to confirm response or if progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Physical exam tumor assessments, photography, pathology/histology and cytology results, as well as, information regarding prior interventions, pre-existing radiographic findings that mimic metastatic disease at baseline/screening and on-study interventions should be captured

in the appropriate eCRFs and may be transmitted to the imaging CRO for additional review if appropriate.

Table 7-2 Imaging collection plan

Procedure	Screening: Day −28 to Day -1	Treatment phase*	End of treatment*	Post-Treatment Phase
CT or MRI (Chest, Abdomen, Pelvis)	Mandated	Every 8 weeks during the first 18 months and every 12 weeks thereafter (± 7 days)	Mandated	Every 8 weeks during the first 18 months and every 12 weeks thereafter (±7 days) until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision (±7 days). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
Brain CT or MRI	Mandated at screening if history of, existing or suspected brain metastases	If brain lesion at screening: every 8 weeks during the first 18 months and every 12 weeks thereafter (± 7 days)	Mandated only if brain lesion at screening	If brain lesion at screening: Every 8 weeks during the first 18 months and every 12 weeks thereafter (±7 days) until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision (±7 days). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
Whole body bone scan**	Mandated, within 42 days (6 weeks) prior to randomization.	As clinically indicated		
Bone X-ray, CT or MRI	Only if skeletal abnormalities identified by whole body bone scan ** at screening, which are not visible in the chest, abdomen, pelvis CT/MRI.	If bone lesion at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (± 7 days)	Mandated only if bone lesion at screening	If bone lesion at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (±7 days) until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision (±7 days). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.

Procedure	Screening: Day −28 to Day -1	Treatment phase*	End of treatment*	Post-Treatment Phase
Skin color Photography	Only if skin lesions at screening	If skin lesions at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (± 7 days)	Mandated if skin lesions at screening	If skin lesions at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (±7 days) until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision (±7 days). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
CT or MRI of any disease outside of chest, abdomen and pelvis (e.g., neck)	Only if suspected lesion at screening	If lesion identified at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (± 7 days)	Mandated if lesion at screening	If lesion identified at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (±7 days) until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision (±7 days). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
*Tumor evaluation at EOT is required for patients who discontinue study treatment before the first scheduled post-baseline tumor assessment (week 8) and for patients whose previous tumor assessment did not demonstrate PD and was done more than 21 days prior to end of treatment visit. ** Whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, sodium fluoride positron emission tomography (NaF PET) or fluorodeoxyglucose (FDG) PET). **Note:** All scans will be acquired and analyzed for primary endpoint locally but should also be sent to the CRO designated by Novartis for central imaging interpretation.				

[redacted]

7.2.1.3 Blinded independent review committee (BIRC) assessment

The primary end point of the study is the local investigator assessed PFS. The BIRC assessed PFS will serve as a supportive evidence of the primary end point. The BIRC will perform an assessment of PFS data for a randomly selected subgroup of patients. An independent random sampling process will select all scans (and relevant information) from approximately 40% of randomized patients, whose BIRC randomization identity will be unknown to the investigators. The central review of the scans will be carried out in a blinded fashion. The decision regarding patient management will remain with the investigators. If consistency of

treatment effect is not established, the BIRC may perform an assessment of PFS data for all patients. Further details regarding BIRC assessment will be provided in the BIRC charter.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examinations, ECOG performance status, height and weight, vital signs, ECG, patient reported outcomes, laboratory assessments (including hematology, chemistry, lipid panel, [redacted] and INR) as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.1.

7.2.2.1 Physical examination

The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site. Physical examination is to be performed according to the visit schedule as outlined in Table 7-1.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's 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 (body temperature, pulse rate, blood pressure) will be monitored as per the visit schedule (see Table 7-1). Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for approximately five minutes.

7.2.2.3 Height and weight

Height and body weight will be measured as outlined in the visit schedule (see Table 7-1).

7.2.2.4 Performance status

The performance status will be assessed according to the ECOG performance status scale (Table 7-3) (Oken 1982) following the schedule given in Table 7-1.

Table 7-3 ECOG performance status

Grade	ECOG status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses (Hematology, Chemistry, Coagulation, Urinalysis, Lipid Panel) are performed by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Visit windows of ± 3 days are allowed for all visits.

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

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

The results of the local laboratory will be recorded in the eCRF if any of the following criteria are met:

- A treatment decision was made based on the local results, or
- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event severity is worse than the one reported by the central lab, or
- There are no concomitant central results available

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 4.0.3. Additional analyses are left to the discretion of the investigator.

Table 7-4 Central 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, urea or BUN, creatinine, fasting glucose, calcium, corrected calcium, magnesium,phosphorous total protein and albumin.

Test Category	Test Name
	AST (SGOT), ALT (SGPT), total bilirubin, direct bilirubin, GGT and alkaline phosphatase, Amylase, lipase and LDH.
Fasting Lipid Panel	Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides
Coagulation	PT, International normalized ratio [INR]
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If there are any significant findings on the dipstick then a microscopic evaluation should be measured: Microscopic Panel (WBC and RBC sediments, Casts, Crystals, Bacteria, Epithelial cells)

[redacted]

7.2.2.5.1 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 7-4.

7.2.2.5.2 Biochemistry

Biochemistry tests are to be performed according to the Visit Schedules outlined in Table 7-1. For details of the biochemistry panel refer to Table 7-4.

7.2.2.5.3 Lipid panel

Lipid panel tests are to be performed according to the Visit Schedules outlined in Table 7-1. For details of the lipid panel refer to Table 7-4.

7.2.2.5.4 Coagulation

Coagulation tests are to be performed according to the Visit Schedules outlined in Table 7-1. For details of the coagulation panel refer to Table 7-4. If the coagulation blood sample collected at screening is clotted when received by central laboratory for testing or the central laboratory results of only the coagulation are delayed, the patient is still eligible to enter the study with a local INR test ≤ 1.5.

7.2.2.5.5 Urinalysis

Urinalysis is to be performed according to the Visit Schedules outlined in Table 7-1. For details of the urinalysis panel refer to Table 7-4.

[redacted]

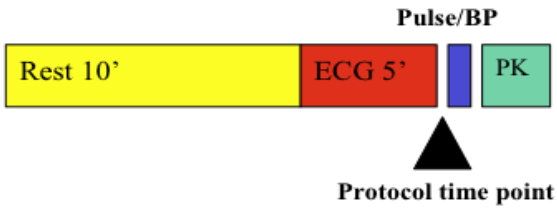
[redacted]

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard triplicate 12 lead ECG assessments will be performed after the patient has been resting for 5-10 min prior to each time point indicated in Table 7-5 below. Triplicate ECGs should be taken approximately 2 minutes apart. The combined QTcF values from these triplicate ECGs will be averaged to provide a single value for each time point. Eligibility will be based on the average of the triplicate ECGs conducted at screening.

Timing of study procedures:



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

Table 7-5 Central ECG collection plan

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

[1]The exact date and time of dosing must be recorded on the appropriate eCRF
[2]ECG assessments are to be done **prior** to PK sampling (if applicable)
[3]Pre-dose ECG on the first day of every cycle. Additionally, 2 h post-dose in every 3rd cycle (i.e. Cycle 9, 12, 15, 18, etc.)

In order for an accurate evaluation of baseline QTcF, a total of three 12-lead ECGs will be performed within 7 days prior to randomization (at screening between Day -7 and Day -1).

Note: In order to ensure ECG evaluation is received from the central laboratory for eligibility assessment, it is advisable to perform the ECG at least 24 hours prior the scheduled randomization date.

If **any of the triplicate readings include** an abnormal ECG as defined in the exclusion criteria or **an average** QTcF value of ≥ 481 ms is obtained at any time after randomization, study treatment must be interrupted, repeat ECG (triplicate) and follow management guidelines detailed in Table 6-6.

An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Additionally, a local cardiologist may be consulted at any time during the study at the discretion of the investigator. If an unscheduled ECG is performed at an external medical facility, a copy of the ECG should be obtained and forwarded to the ECG central laboratory, and a copy kept in the source documents at the study site. Centrally reviewed ECG findings should be documented on the ECG CRF page.

In the event that a QTcF value of ≥501ms is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the

time and date of the last study drug intake to determine the drug exposure. If PK sampling is possible, refer to the section PK sampling and detail appropriate procedures to be followed (Section 7.2.3).

All ECGs including unscheduled triplicate ECGs with clinically relevant findings, collected during the study should be transmitted to the central laboratory and will be centrally reviewed by an independent reviewer. The results of the centrally assessed ECGs are electronically transferred into the clinical database.

Any original ECG not transmitted to a central laboratory should be forwarded for central review. Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening when the patient signed informed consent should be reported on the Medical History CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.2.6.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

Cardiac imaging will be performed by MUGA scan or ECHO in order to assess the left ventricular ejection fraction. This assessment will be performed according to the schedule given in Table 7-1.

The same technique (MUGA or ECHO) must be used during the course of the trial, and the method used will be recorded in the eCRF. Only clinically significant abnormalities should be reported in the Adverse Events eCRF.

In case a patient develops left ventricular systolic dysfunction while on study treatment dose adjustment guidelines described in Table 6-7 must be followed.

7.2.3 Pharmacokinetics

Pharmacokinetic blood samples will be obtained from all patients for the analysis of ribociclib (and any relevant metabolites such as LEQ803). Patients will be assigned to the sparse PK collection group or the trough PK collection group.

- Sparse PK collection group: In the sparse PK group, approximately the first 150 patients enrolled will have PK collections as described in Table 7-6.
- Trough PK collection group: In all remaining patients, PK collections will be collected as described in Table 7-7.

Meal conditions (fasting, low fat, high fat) will be recorded within ± 30 minutes of a dose on the meal record eCRF page for patients assigned to the sparse PK collection group on Cycle 1 Day 15 and Cycle 2 Day 15; the impact of meal conditions on PK in patients may be explored. Refer to Section 6.1.1.2 and Section 10.6.3 for details.

An unscheduled PK blood sample may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion. If a patient discontinues from the study treatment due to toxicities related to study treatment, an

unscheduled PK blood sample may be obtained as soon as possible after the last dose and the date and time of last dose recorded. In addition, an unscheduled blood sample may be collected if additional ECG measurements are conducted.

The date and exact time of dosing on PK collection days, as well as the date and actual time of blood sampling must be recorded on the appropriate eCRF pages. In addition, the exact time of dosing on the previous day must be precisely recorded.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed, and medication should resume on the next day. The occurrence and frequency of any vomiting must be noted in the adverse events section of the eCRF. In addition, the date and exact time of vomiting should only be recorded if it occurs within 4 hours of dosing on the days of PK sampling. If a vomiting episode occurs within the first 4 hours post-dosing during the day of the last dose prior to trough PK samples the exact time (whenever possible) must be noted on the eCRF.

A detailed description of the planned analyses for PK is given in Section 10.5.4.

7.2.3.1 Pharmacokinetic blood sample collection and handling

Blood samples will be obtained from all patients either by direct venipuncture or through an indwelling cannula (e.g., inserted in a forearm vein, or central venous line) for the analysis of plasma concentrations of ribociclib (and any relevant metabolites such as LEQ803), when feasible. At the specified time points described in Table 7-6 and Table 7-7, one single 3mL blood draw will be collected into a tube containing EDTA and gently inverted several times to thoroughly mix the anticoagulant. The blood tube will be centrifuged to separate the plasma. Plasma will immediately be split and transferred into separate pre-labeled tubes for ribociclib. Plasma samples will be stored frozen in an upright position until shipment.

Any sampling problems (e.g., patient took study drug before blood sample, scheduled sampling time is missed, sample is not drawn according to the schedule) should be noted as a comment on the eCRF.

Refer to the [Central Laboratory documents] for detailed instructions for the collection, handling, and shipment of PK samples.

Table 7-6 Sparse pharmacokinetic blood collection log

Note: Sparse PK sampling will be performed on approximately the first 150 patients in this study. Blood for Sparse PK profiling will be collected on C1D15 and C2D15 at Pre-dose (0), 2, 4, 6hr, and C2D1 Pre-dose (0hr) for ribociclib/placebo. Only for the sparse PK group, the meal condition (fasting, low fat, high fat) will be collected within ± 30 minutes of the dose on the eCRF on days C1D15 and C2D15.

Cycle	Day	Scheduled Time Point Relative to Dosing	DRID No. for ribociclib/ placebo	PK Sample No. for ribociclib/ placebo	Blood Volume (mL)
1	15	Pre-dose[a]	101/1001[d]	101	3
		2h post-dose (± 15 min)	101	102	3
		4h post-dose (± 15 min)	101	103	3
		6h post-dose (± 15 min)	101	104	3
2	1	Pre-dose[a]	102	105	3
	15	Pre-dose[a]	103/1003[d]	106	3

Note: Sparse PK sampling will be performed on approximately the first 150 patients in this study. Blood for Sparse PK profiling will be collected on C1D15 and C2D15 at Pre-dose (0), 2, 4, 6hr, and C2D1 Pre-dose (0hr) for ribociclib/placebo. Only for the sparse PK group, the meal condition (fasting, low fat, high fat) will be collected within ± 30 minutes of the dose on the eCRF on days C1D15 and C2D15.					
		2h post-dose (± 15 min)	103	107	3
		4h post-dose (± 15 min)	103	108	3
		6h post-dose (± 15 min)	103	109	3
Unscheduled		Anytime[b]	NA	1001+	3
		PK samples related to a QTcF ≥ 501 ms[c]	NA	1051+	3
a. Collect Pre-dose PK sample immediately before drug administration (approximately 24-hrs after the last dose and immediately before the next dose) b. Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely, sequentially numbered 1001, 1002, etc., for ribociclib/placebo c. Unscheduled PK samples related to a QTcF ≥ 501 ms will be uniquely, sequentially numbered 1051, 1052, etc., ribociclib/placebo d. The first dose reference ID (DRID) No. is for the current dose, while the second DRID No. is for the last dose the subject received prior to the collection of the PK sample					

Table 7-7 Trough pharmacokinetic blood collection log

Note: Trough PK sampling will be performed in all remaining patients Pre-dose on C1D15, C2D1 and C2D15.					
Cycle	**Day**	**Scheduled Time Point Relative to Dosing**	**DRID No. for ribociclib/ placebo**	**PK Sample No. for ribociclib/ placebo**	**Blood Volume (mL)**
1	15	Pre-dose[a]	201/2001[d]	201	3
2	1	Pre-dose[a]	202	202	3
	15	Pre-dose[a]	203/2003[d]	203	3
Unscheduled		Anytime[b]	NA	2001+	3
		PK samples related to a QTcF ≥ 501ms[c]	NA	2051+	3
a. Collect Pre-dose PK sample immediately before drug administration (approximately 24-hrs after the last dose and immediately before the next dose) b. Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely, sequentially numbered 2001, 2002, etc., for ribociclib/placebo c. Unscheduled PK samples related to a QTcF ≥ 501 ms will be uniquely, sequentially numbered 2051, 2052, etc., ribociclib/placebo d. [d.] The first DRID No is for the current dose, while the second DRID No is for the last dose the subject received prior to the collection of the PK sample					

Additional guidelines for pharmacokinetic sampling/ECG

On days with PK sampling and/or ECG testing (collection days are outlined in Table 7-1), the following additional guidelines must be followed:

- Pre-dose ECGs must be done **first**, **prior to pre-dose PK sampling and prior to dosing**.
- The time of PK collection and the time the study medication was taken must be precisely recorded in the eCRF.
- Furthermore, the date and time the study medication was taken on the **day before** the PK collection must be precisely recorded in the eCRF.

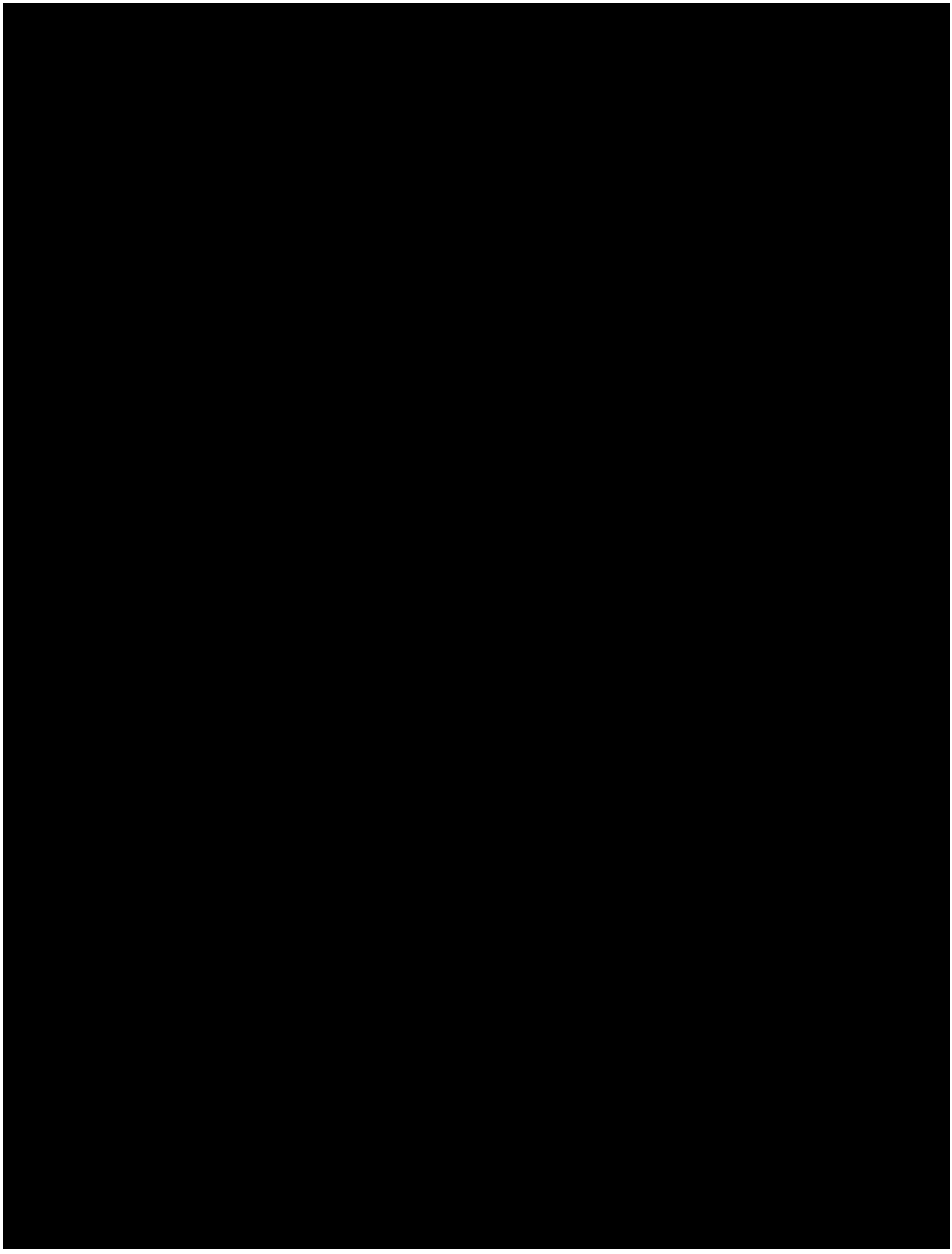
- Post-dose ECGs and/or PK samples should be collected after dosing of the study treatment. ECGs must be done prior to PK sampling.
- ECG and PK sample collection will be performed according to Section 7.2.3 and Table 7-5, Table 7-6 and Table 7-7.
- In the case where ribociclib/placebo is being temporarily interrupted or has been permanently interrupted, no PK samples will be collected for the corresponding visit.

7.2.3.2 Analytical method

Plasma concentrations of ribociclib (and any relevant metabolite such as LEQ803) will be measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods with a lower limit of quantification (LLOQ) of approximately 1.0 ng/ml for ribociclib. Sample analysis will be performed by Novartis or a Novartis designated laboratory using validated methods. Any results below the LLOQ and any missing samples will be recorded accordingly.

[redacted]

[redacted]



7.2.6 Patient reported outcomes

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0), the EuroQoL 5-level instrument (EQ-5D-5L, tablet version), and the Brief Pain Inventory-Short form questionnaire (BPI-SF, copyright 1991) will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms, treatment-related side effects, global health status, and cancer-related pain. The EORTC QLQ-C30, EQ-5D-5L, and BPI-SF are recognized reliable and valid measures (Aaronson 1993, Rabin 2001, Cleeland 1994) frequently used in clinical trials of patients with advanced or metastatic breast cancer.

All patient-reported outcome (PRO) measures (eg, EORTC QLQ-C30, EQ-5D-5L, and BPI-SF) will be administered before any study drug administrations at the visits indicated in Table 7-1 and Table 7-9. Collection of PRO measures have a ± 7 day window unless otherwise indicated.

All PRO data will be collected using an electronic tablet device and should be administered in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient's perspective. Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all patients, including from those who discontinue prior to the study evaluation completion visit, however, if patients refuse to complete questionnaires, this should be documented in study source records. Patient's refusal to complete study questionnaires are not protocol deviations.

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

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

Table 7-9 Patient reported outcomes collection plan

Patient Questionnaire	Cycle	Visit	Time
EORTC QLQ-C30 EQ-5D-5L BPI-SF	Screening	-28 to Day -1	Prior to any clinical assessments, drug dosing or diagnostic testing
	Subsequent cycles	Every 8 weeks after randomization during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision	
	End of treatment	Day of EOT visit	

Patient Questionnaire	Cycle	Visit	Time
	Efficacy follow-up	Every 8 weeks after randomization during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision	

7.2.6.1 EORTC QLQ-C30

The EORTC QLQ-C30 contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale (Aaronson et al 1993).

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual (Fayers et al 2001).

7.2.6.2 EQ-5D-5L

The EQ-5D-5L (tablet version) is a standardized measure of health utility that provides a single index value for one's health status. The EQ-5D-5L is frequently used for economic evaluations of health care and has been shown to be a valid and reliable instrument (The EuroQol Group 1990, Rabin 2001). The EQ-5D-5L contains one item for each of five dimensions of HRQOL (i.e., mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). Response options for each item vary from having no problems (e.g., "…no problems walking about"), moderate problems (e.g., "…some problems walking about"), or extreme problems (e.g., "…unable to walk about"). Patient responses to the five dimensions of HRQOL reflect a specific health state that corresponds to a population preference weight for that state on a continuous scale of 0 (death) to 1 (perfect health). A visual analog scale (ranging from 0 to 100) is also included to capture patient's rating of their overall health status. Higher scores of the EQ-5D-5L represent better health states. All scoring and handling of data will follow the User's Guide defined by the EuroQoL Group (Oemar and Janssen 2013).

7.2.6.3 Brief Pain Inventory-Short Form

The BPI-SF is a short, self-administered 11-item questionnaire designed to evaluate the intensity of and impairment caused by cancer pain. All questions in the BPI-SF are scored using an 11-point rating scales. Four questions measure pain intensity (pain now, average pain, worst pain, and least pain) using 0 ("no pain") to 10 ("pain as bad as you can imagine") numeric rating scales; and seven additional questions measure the level of interference caused by pain (general activity, mood, walking ability, normal work, relations with other persons,

sleep, and enjoyment of life) using 0 (no interference) to 10 (complete interference) rating scales.

Questions from the BPI-SF are aggregated into a pain severity index defined based on the sum of four items focused on pain intensity, and pain interference indices defined as subscale scores of pain interference with activity (interference with walking, general activity and work) and affect (interference with relations with others, enjoyment of life and mood) and an overall interference score (all seven items) (Cleeland 1994). Missing values will be handled as recommended by the developers of the BPI-SF (Cleeland 2009). All four severity items must been completed for aggregating a pain severity index. The pain interference indices are scored as the mean of the item scores multiplied given that more than 50%,of the items have been completed.

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 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 ('but is collected as seriousness criteria'); rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination,

laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

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

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

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), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events 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 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  a. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  b. 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.
  c. Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

8.2.2 Reporting

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

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

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

Follow-up information is submitted in the same way the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken for safety reasons when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, patient number and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

Study treatment must be discontinued once emergency unblinding.

8.4 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 Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator 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.

8.6 Data monitoring committee

An independent data monitoring committee (IDMC) will be established to assess the safety results of ribociclib in an unblinded manner. The IDMC will be responsible for reviewing the safety results and overseeing the safety data accruing in the trial at regular intervals of approximately every six months, provided that sufficient patients have been randomized. Also, if requested by the IDMC Chair, additional safety reviews may be performed.

The IDMC will consist of at least two oncologists and one biostatistician and will be formed prior to the randomization of the first patient. Detailed recruitment status and interim safety reports will be provided to the IDMC on a regular basis. Recruitment will not be interrupted. Details will be provided in the IDMC charter.

8.7 Steering committee

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

The SC will be an advisory board for the study according to the protocol through recommending modifications as circumstances require. The SC will be consulted for protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop

recommendations for publications of study results. The details of the role of the SC will be defined in a SC charter. The SC will not have access to unblinded trial data.

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.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

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

For studies using Electronic Data Capture (EDC), 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.

Blood and tumor samples for laboratory data, PK and [redacted] will be collected by sites and sent to the Novartis designated central laboratory for processing. The laboratory results and IRT data will be sent electronically to Novartis. Imaging and ECG data will be collected at the sites and the data will be transmitted to a designated CRO for centralized analysis, as well as further processing. PRO data will be recorded by patients onto the electronic tablet device maintained at the study site. The device will be programmed to ensure that all relevant observations are recorded.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel 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 is 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.

Samples and/or data (e.g. PK, [redacted],ECG, imaging, safety samples) will be processed centrally and the results will be sent electronically to Novartis. PRO data collected using an electronic tablet device will be documented into a separate study-specific database supplied and managed by a designated vendor. The PRO database will be accessible to study sites and Novartis personnel (or a designated CRO) for data management. All PRO data will be sent electronically to Novartis personnel (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

10 Statistical methods and data analysis

It is planned that the data from all centers participating in the trial will be combined, so that an adequate number of patients are available for analysis. Novartis and/or a designated CRO will perform all analyses.. Any data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation.

10.1 Analysis sets

10.1.1 Full analysis set

The FAS comprises all randomized patients. Following the ITT principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

10.1.2 Safety set

The Safety Set includes all patients who received at least one dose of study medication defined as fulvestrant, or ribociclib/placebo and had at least one post-baseline safety assessment. Patients will be analyzed according to the study treatment they actually received. Actual treatment refers to the treatment that the patient was randomized to, unless the alternative treatment was received throughout the trial. Please note: the statement that a patient had no adverse events (on the Adverse Event eCRF) constitutes a valid safety assessment.

10.1.3 Per-protocol set

The per-protocol set (PPS) will include the subset of the patients in the FAS without major protocol deviations. All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the data handling plan and analysis plan. Sensitivity analyses of the primary endpoint of PFS may be performed using data from the PPS if the FAS and PPS differ and if the primary analysis is significant.

10.1.4 Pharmacokinetic analysis set

The PK Analysis Set (PAS) will consist of all patients who receive at least one dose of study treatment (ribociclib/placebo or fulvestrant) and have at least one evaluable post-dose concentration measurement.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristic/prognostic data will be summarized descriptively by treatment group using data from the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below.

The actual dose and duration of fulvestrant, and ribociclib/placebo treatment, as well as dose intensity (computed as the ratio of actual dose received to actual duration) and the relative dose intensity (computed as the ratio of the dose intensity to planned dose received/planned duration), will be listed and summarized using descriptive statistics. The total daily doses of fulvestrant and ribociclib/placebo for each patient will be summarized using descriptive statistics (e.g. mean, median, and mode).

Concomitant medications and significant non-drug therapies will be listed by patient and summarized by ATC (Anatomical Therapeutic Chemical classification system) term for each treatment group. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions.

10.4 Primary objective

The primary objective in the study is to determine whether treatment with fulvestrant + ribociclib prolongs PFS compared to treatment with fulvestrant + ribociclib placebo in men and postmenopausal women with HR+, HER2- advanced breast cancer who received no or only 1 line of prior hormonal therapy for advanced breast cancer.

10.4.1 Variable

The primary efficacy endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. If a patient has not had an event, PFS will be censored at the date of the last adequate tumor assessment (see RECIST 1.1 in Appendix 2 for further details). Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. PFS will be assessed via a local radiology assessment according to RECIST 1.1.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be the comparison of PFS between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance.

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

$H01: \theta 1 \geq 0$ vs. $Ha1: \theta 1 < 0$

where $\theta 1$ is the log-hazard ratio (fulvestrant+ribociclib arm vs. fulvestrant + placebo arm) of PFS.

The primary efficacy endpoint PFS will be analyzed at the interim look/analysis and final look of a group sequential design based on the FAS population according to the treatment group patients were randomized to and the strata they were assigned to at randomization (strata formed using the randomization factor as obtained via IRT). PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented by treatment group.

10.4.3 Handling of missing values/censoring/discontinuations

PFS will be censored if no PFS event is observed before the cut-off date. The censoring date will be the date of last adequate tumor assessment before cutoff date. If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used (see RECIST 1.1 Appendix 2).

10.4.4 Supportive analyses

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

The primary analysis for PFS may be repeated with data based on PPS if the primary analysis is statistically significant. Other sensitivity analyses may be performed such as (1) including PFS events even if the events are recorded after two or more missed assessments, (2) backdating events occurring after missing tumor assessments.

Subgroup analyses will be performed on each level of stratification factors if the primary analysis is significant. The analysis will include Kaplan-Meier summaries and estimation of hazard ratios from un-stratified Cox regression models. Additional subgroup analyses to assess the homogeneity of treatment effect based on demographic and baseline disease characteristics may be performed; details about the subgroups to be included will be provided in the study analysis plan.

Patterns of censored data will be examined by the treatment groups using descriptive statistics (the numbers of censored patients and reasons for censoring).

PFS assessed by BIRC will serve as supportive evidence of the primary end point. Two methods will be used to summarize the data from the BIRC assessment. The NCI (National

Cancer Institute) method (Dodd et al. 2011), uses an auxiliary variable estimator of the log-hazard ratio that combines information from patient-level investigator assessment from all patients and the BIRC assessment of patients randomly selected for central review. This estimate and its one-sided 95% CI will be provided. Details of the audit sample size calculation for the BIRC assessment are provided in Section 10.8. The NCI method will be used for audit sample size determination and summary of treatment effect (HR, 95% confidence intervals) based on the supportive BIRC assessment.

The data from the BIRC assessment generated following the sampling scheme as above will also be summarized using the method proposed by Amit et al. 2011, referred to as the PhRMA (Pharmaceutical Research and Manufacturers of America) method. With this approach, the DD (differential discordance) of early discrepancy rate (EDR) and late discrepancy rate (LDR) between the two arms will be estimated as the rate on the fulvestrant+ribociclib arm minus the rate on the fulvestrant+placebo arm. The EDR and LDR results will also be summarized by treatment arm. [redacted]

10.5 Secondary objectives

The secondary objectives in this study are to compare the two treatment groups with respect to overall survival (OS), and evaluate overall response rate (ORR), clinical benefit rate (CBR), time to response (TOR), duration of response (DOR) and time to definitive deterioration in the quality of life and ECOG PS, safety. OS between the 2 treatment arms will be statistically compared. A hierarchical testing strategy will be taken to control overall type-I error rate; therefore OS will be statistically evaluated and interpreted only if the primary efficacy endpoint PFS is significantly different between the 2 treatment groups.

10.5.1 Overall Survival

One of the secondary objectives of the study is to determine whether treatment with fulvestrant + ribociclib prolongs overall survival (OS) compared to treatment with fulvestrant + placebo.

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

Assuming proportional hazards model for OS, the following statistical hypothesis for OS will be tested using a stratified log-rank test (stratified according to randomization stratification factors) at the one-sided 2.5% level of significance:

$H02: \theta 2 \geq 0$ vs. $Ha2: \theta 2 < 0$

where $\theta 2$ is the log-hazard ratio (fulvestrant+ribociclib arm vs. fulvestrant+placebo arm) of OS.

The analyses for OS will be based on the FAS. The distribution of OS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance.

The final OS analysis will not be performed at the time point of the final PFS analysis, but after additional follow-up. Therefore, a four-look design is considered for OS.

1. OS will be hierarchically tested (provided the primary PFS analysis is statistically significant)in the following way.The first potential time point for OS analysis will be at the time of the primary PFS analysis at which time approximately 161 deaths are expected. If PFS is statistically significant at this stage, OS will also be tested. If OS is not statistically significant at this stage, the 2nd OS analysis is planned after approximately 263 deaths are expected. If OS is not statistically significant at this stage, the final OS analysis will be planned after approximately 351 deaths.

The type I error probability for OS tests will be controlled by using a separate Lan-DeMets (O'Brien-Fleming) alpha spending function independent of the one used for the primary efficacy analysis of PFS at the one-sided type I error of α=0.025. This guarantees the protection of the overall level α = 2.5% across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses (Glimm 2010).

The distribution function of OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals will be presented by treatment group. The stratified Cox regression will be used to estimate the hazard ratio (HR) of OS, along with 95% confidence interval.

10.5.2 Other secondary efficacy objectives

10.5.2.1 Overall response rate

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

ORR will be calculated based on the FAS according to the ITT principle; however patients with only non-measurable disease at baseline will be included in the numerator if they achieve a complete response. ORR will be presented by treatment group along with approximate 95% confidence intervals. The Cochran-Mantel Haenszel chi-square test (stratified by baseline stratification factor) will be used to compare the two treatment groups with respect to the ORR at one-sided 2.5% level of significance. As a supportive analysis, ORR as assessed by the blinded independent central review will be calculated by treatment group and presented along with the approximate 95% confidence intervals. As a sensitivity analysis, ORR for patients with measurable disease at baseline will be calculated and presented by treatment group together with approximate 95% confidence intervals.

10.5.2.2 Clinical benefit rate

Clinical Benefit is defined as CR, PR or SD for 24 weeks or longer. CR, PR and SD are defined according to RECIST 1.1. CBR will be calculated based on the FAS; however patients with only non-measurable disease at baseline will be included in the numerator if they achieve a complete response. CBR will be summarized for the two treatment groups using descriptive statistics. The Cochran-Mantel Haenszel chi-square test (stratified by baseline stratification factor) at 2.5% one-sided level of significance, will be used to compare the two treatment groups with respect to the CBR. As a supportive analysis, CBR as assessed by the

blinded independent central review will be summarized for the two treatment groups using descriptive statistics.

10.5.2.3 Time to response

Time to response is the time from the date of randomization to the first documented response (CR or PR, which must be confirmed subsequently) according to RECIST 1.1. All patients will be included in time to response calculations. Patients who do not achieve a confirmed response will be censored at the maximum follow-up time (i.e. first patient first visit to last patient last visit used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause) or at the date of last adequate tumor assessment. Time to response data will be listed and summarized by treatment group. The distribution of time to response may be summarized through Kaplan-Meier method if sufficient number of events are observed.

10.5.2.4 Duration of response

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

10.5.2.5 ECOG performance status

ECOG PS scale as described in Section 7.2.2.4 will be used to assess physical health of patients. An analysis of time to definitive deterioration of the ECOG PS by one category of the score from baseline will be performed. Deterioration is considered definitive if no improvements in ECOG PS status is observed at a subsequent time of measurement during the treatment period following the time point where the deterioration is observed.

Patients receiving any further therapy prior to definitive worsening will be censored at their date of last assessment prior to start of therapy. Patients that have not worsened at the data cut-off point will be censored at the date of last assessment prior to start of therapy. Kaplan-Meier method will be used to estimate the distribution of time to definitive worsening and median time to definitive worsening will be presented along with a 95% confidence interval. A stratified log-rank test at one-sided 2.5% level of significance will be used to compare the distribution of time to definitive worsening between the 2 treatment arms.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

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

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 31 after last dose of study medication.

10.5.3.2 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 treatment group.

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

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

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

10.5.3.3 Laboratory abnormalities

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.

In some cases (e.g., white blood cell differentials), the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinical meaningful limit expressed in absolute counts.

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.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

- classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, [redacted]

10.5.3.4 Other safety data

10.5.3.4.1 ECG

- shift table from baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

10.5.3.4.2 Vital signs

- shift table from 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.

10.5.3.5 Tolerability

Tolerability will be studied in terms of dose reductions and drug interruptions due to AE. Reasons for dose reductions and interruptions will be listed and summarized by treatment.

10.5.4 Pharmacokinetics

PK concentrations of ribociclib (and any relevant metabolites such as LEQ803) will be summarized by time point using descriptive statistics by treatment only for fulvestrant + ribociclib arm. All PK concentration data will be listed as appropriate.

10.5.4.1 Data handling principles

Plasma samples will be assayed for ribociclib concentrations by Novartis or Novartis designated laboratory using validated LC-MS/MS methods with a LLOQ of approximately 1.00 ng/mL for ribociclib.

All concentrations below the LLOQ will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV. Any missing PK parameter data will not to be imputed.

10.5.5 Patient-reported outcomes

The EORTC QLQ-C30 questionnaire and the EuroQol EQ-5D-5L will be used to collect patient's QoL data. The BPI-SF will be used to assess patient's subjective assessment of cancer-related pain. The global health status/QoL scale score of the QLQ-C30 is identified as the primary patient-reported outcome variable of interest. Physical functioning, emotional functioning and social functioning scale scores of the QLQ-C30, the health status index score and overall health status of the EQ-5D-5L, and worst pain item (based on question 3), pain

severity index, and pain interference indices of the BPI-SF are identified as secondary patient-reported QoL variables of interest.

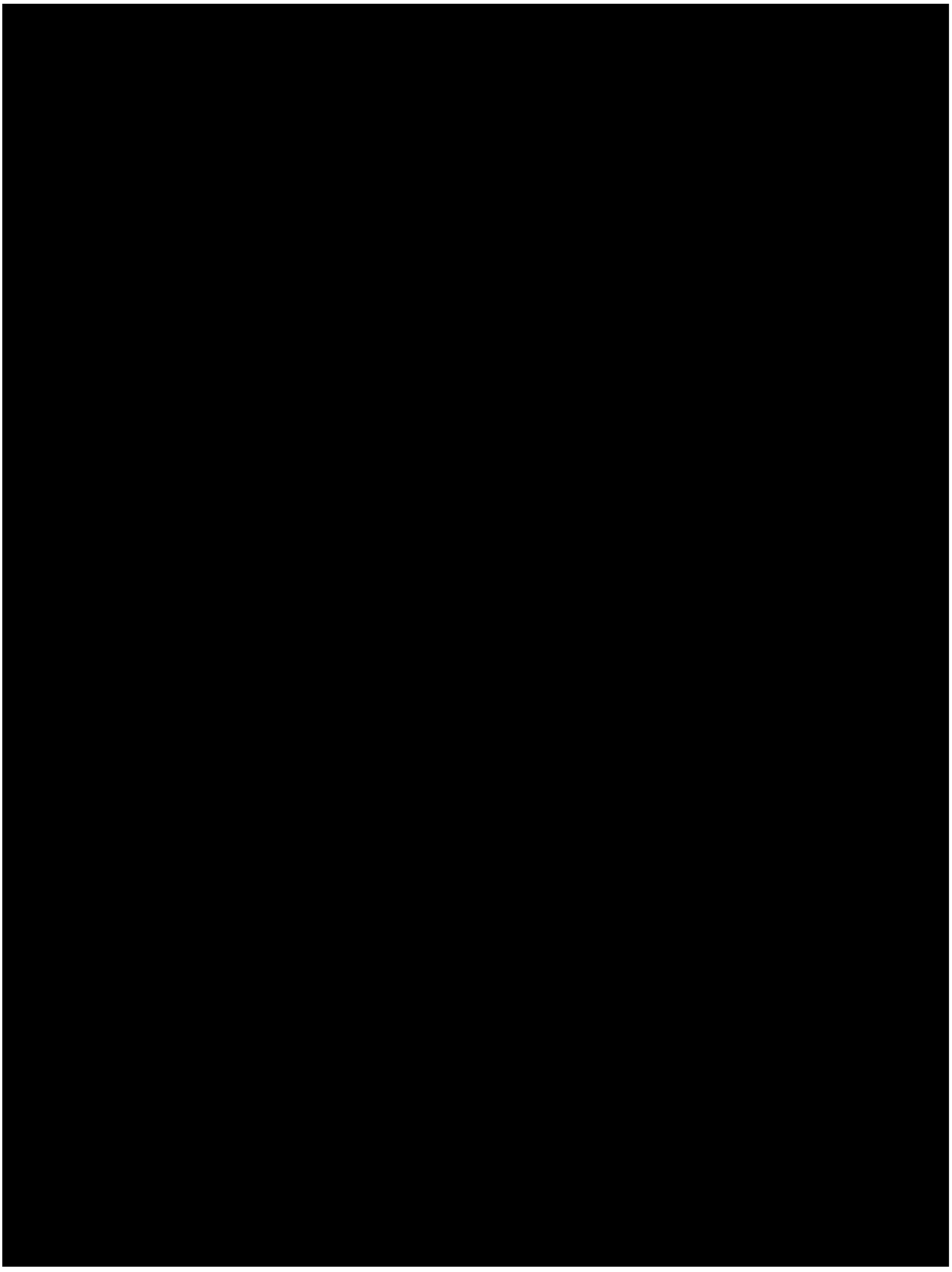
Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective patient questionnaire (Fayers 2001; Oemar and Janssen 2013; Cleeland 2009). No imputation procedures will be applied for missing items or missing assessments. Five health states from the EQ-5D-5L will be converted to index values during the data analysis stage and will be further defined in the analysis plan. In addition, the visual analog scale (ranging from 0 to 100) will be evaluated for patient's rating of their overall health status.

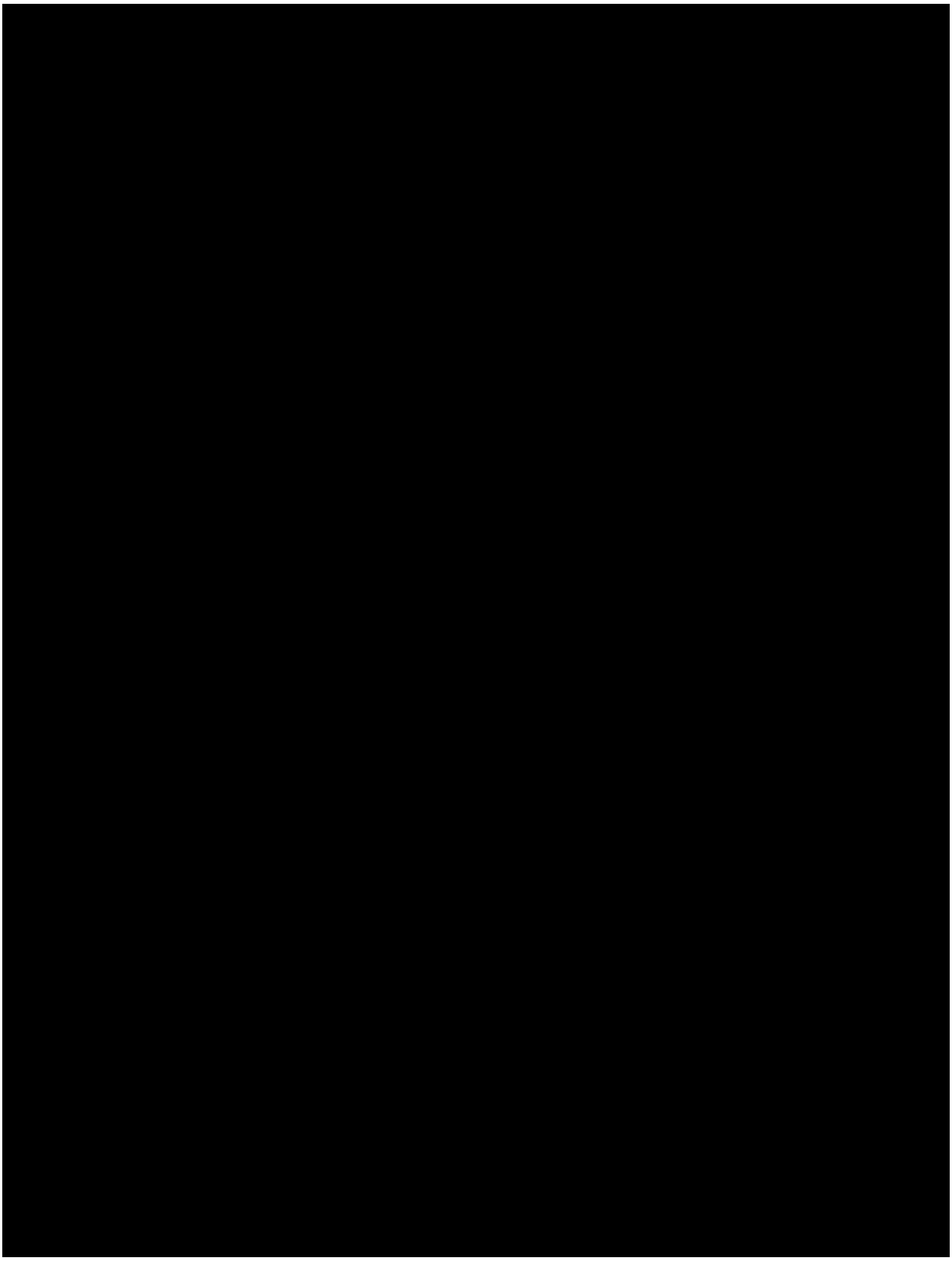
The number of patients completing the each questionnaire and the number of missing or incomplete assessments will be summarized by treatment group for each scheduled assessment time points for each cohort. No formal statistical tests will be performed of PRO data and hence no multiplicity adjustment will be applied. The FAS will be used for analyzing PRO data.

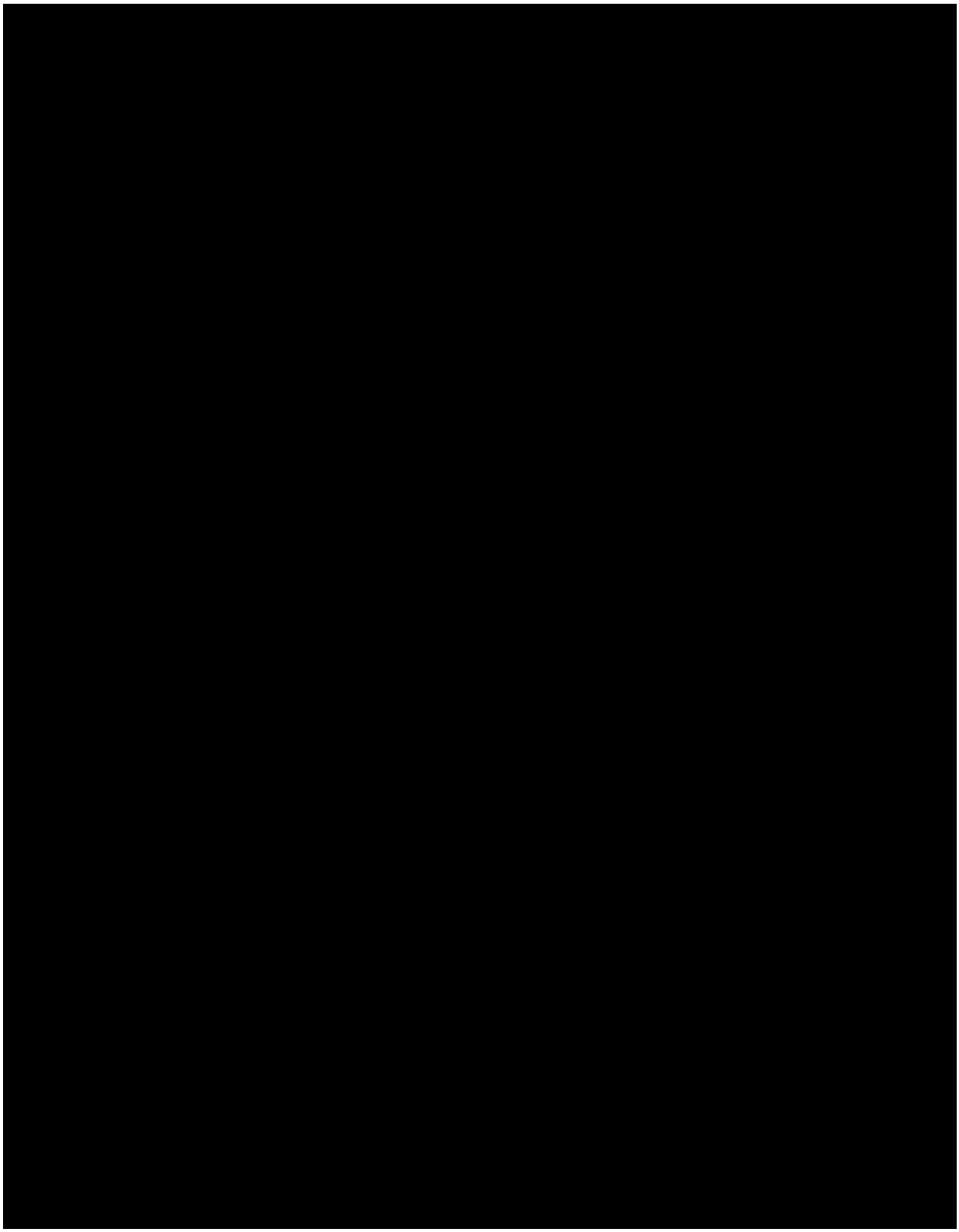
Descriptive statistics will be used to summarize the scored scales of the QLQ-C30; health states, overall health status, and index values of the EQ-5D-5L, and the worst pain item (question 3), pain severity index, and pain interference indices of the BPI-SF at each scheduled assessment time point for each cohort. Additionally, change from baseline in the domain scores, health states, overall health status, and index values at the time of each assessment will be summarized. Shift tables will be produced to describe worsening of pain from baseline based on the worst pain item from the BPI-SF. 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.

In addition, a repeated measurement analysis model may be used to compare the two treatment groups with respect to changes in the domain scores (global health status/QoL scale score, physical functioning, emotional functioning and social functioning scale scores of the QLQ-C30 index score and overall health status of the EQ-5D-5L, longitudinally over time. [redacted]

Time to definitive 10% deterioration in the global health status/QoL, physical functioning, emotional functioning, social functioning will be assessed. The time to definitive 10% deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% relative to baseline worsening of the corresponding scale score or death due to any cause. If a patient has not had an event, time to deterioration will be censored at the date of the last adequate QoL evaluation. The distribution will be presented descriptively using Kaplan-Meier curves. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to definitive 10% deterioration along with two-sided 95% confidence interval. Additionally, time to definitive deterioration with different cutoff definitions (e.g. 5%, 15%) may be specified in the RAP as deemed appropriate. A stratified Cox regression will be used to estimate the hazard ratio (HR), along with two-sided 95% confidence interval.







[redacted]

10.7 Interim analysis

10.7.1 Progression free survival

No PFS interim analysis is planned in this study.

10.7.2 Overall survival (OS)

OS will be compared between the two treatment groups, provided the primary endpoint PFS is statistically significant favoring the test treatment arm (ribociclib + fulvestrant). A gatekeeping testing procedure will be adopted in this study and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant. A maximum of 3 analyses is planned for OS; at the time of the final analysis for PFS (provided PFS is significant), at which point approximately 161 deaths are expected, after approximately 263 events have been documented), and a final analysis for OS when approximately 351 deaths are expected (expected 56 months from date of first patient to be randomized).

An α-spending function according to Lan-DeMets (O'Brien-Fleming) independent of the one used for the primary efficacy analysis, (as implemented in East 6.3) along with the testing strategy outlined below will be used to maintain the overall type I error probability (Lan and DeMets 1983). This guarantees the protection of the 2.5% overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analysis (Glimm 2010). The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint PFS has already been shown to be statistically significant favoring the test treatment arm (ribociclib +fulvestrant). Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

The projected timing of interim analysis is summarized in Table 10-1.

Table 10-1 Estimated timelines for interim and final analyses

Months after randomization of the first patient	PFS events	Power (%) against a hazard ratio of 0.67	OS events	Cumulative Conditional Power (%) against hazard ratio of 0.71

Months after randomization of the first patient	PFS events	Power (%) against a hazard ratio of 0.67	OS events	Cumulative Conditional Power (%) against hazard ratio of 0.71
26	364 (100%)	90	161(46%)	14
39	--	--	263(75%)	60
56	--	--	351(100%)	85

Statistical significance of OS will only be declared if significance for primary PFS analysis has been declared.

At the time of final PFS analyses, both PFS and interim OS analysis will be performed by the Sponsor's clinical team. Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

10.8 Sample size calculation

The median time to progression (TTP) for fulvestrant in first line post-menopausal advanced breast cancer patients is estimated to be between 8 month (Howell 2004) and 23 months in FIRST trial (Robertson et al 2012). For sample size calculation, the median PFS for 1st line patients is assumed to be 18 month. The median PFS for fulvestrant in relapsed advanced breast cancer is estimated to be between 4.8 months (SoFEA trial, Johnston et al 2013) and 6.5 months (CONFIRM trial, Di Leo et al 2010). Since the study population is closer to the population in CONFIRM trial, for sample size calculation, the mPFS for fulvestrant in second line is assumed to be 6.5 months. It is assumed that 40% and 60% of the patients will be from first line and second line respectively. The median PFS in the control arm (fulvestrant + placebo) is estimated via simulation to be around 9 months. It is hypothesized that the addition of ribociclib will result in a clinically meaningful 33% reduction in the hazard rate of PFS, corresponding to an increase in median PFS to 13.4 months. A maximum of 364 PFS events will be required to detect a hazard ratio of 0.67 with 95% power using the log-rank test at one-sided cumulative 2.5% level of significance (EAST 6.3). The increase in power from 90% to 95% while targeting the same hazard ratio and the number of events as in the original protocol is primary due to the elimination of the futility interim analysis. Assuming that enrollment will continue for approximately 19 months at a uniform rate and 10% dropout rate by the time of PFS final analysis, a total of 660 patients should be randomized to the two treatment groups in 2:1 ratio to observe 364 events at approximately 7 months following the randomization of the last patient, i.e., 26 months from the randomization date of the first patient in this study. The sample size calculation was conducted with software package East 6.3. The sample size calculations are based on the estimates from data available from prior studies. A mid-study sample size re-assessment based on blinded pooled data may be performed prior to any efficacy analysis if data from the study indicate substantial deviation from the study assumptions.A Monte-Carlo simulation based on 10,000 samples was carried out to characterize the probability of the study outcomes under various assumptions of the true hazard ratios (Table 10-2). If the alternative hypothesis is true, that is, the true hazard ratio is 0.67, then there is 96% probability the primary analysis will be statistically significant.

Table 10-2 Probability of Study Outcomes under various true Hazard Ratios

True Hazard Ratio	% statistical significance*
0.5	100
0.6	99.7
0.67	96
0.7	91
0.8	53
0.9	16
A total of 660 patients will be enrolled with exponential dropout hazard rate 0.0105 (about 10% drop out rate) *: Based on 10,000 simulations using EAST 6.3	

The primary objective of the study is to compare investigator assessed PFS between arms in the overall population (both 1st line and 2nd line patients). If the primary analysis is statistically significant, treatment effect will be evaluated in 1st and 2nd line patients separately. Based on the estimated median PFS and proportion of patients in 1st line and 2nd line respectively, it is expected that the accumulation of events in 1st line will be slower than 2nd line patients. To ensure enough information coming from 1st line patients, the final analysis will be done after approximately 125 events in the first line patients or approximately 364 events in both arms whichever comes later.

Audit size for BIRC assessed PFS

The audit size of the sample-based BIRC assessment will be 40% of all randomized patients. Based on the audit size calculation approach proposed by Dodd, et. al (2011), assuming investigator and BIRC assessments are similar and the estimated log of investigator-based HR is -0.40 (i.e., HR=0.67), the audit size of 40% will ensure that the upper bound of a one-sided 95% CI for BIRC-based log-hazard ratio has 86% probability of being below 0 (i.e. HR < 1) if the correlation between investigator assessment and BIRC assessment is 0.7 (the estimated correlation based on data from the BELLE-2 [CBKM120F2302] study in metastatic breast cancer).

Power for analysis of overall survival

OS will be compared between the two treatment arms, provided that the primary endpoint, PFS, is statistically significant. The power statements for overall survival below are therefore conditioned on significant primary PFS result. Estimate of first line median OS with fulvestrant alone is not published. However the median OS with fulvestrant alone in first line setting is expected to be between 34 months (letrozole alone, Mouridsen 2003) and 38 months (anastrozole alone, FACT trial, Bergh et al 2012) based on results from endocrine based monotherapy studies. For sample size calculation, we assume the median OS for fulvestrant alone in first line to be 38 month. Median OS for fulvestrant in relapsed post-menopausal advanced breast cancer patients is estimated to be between 19 months (SoFEA trial, Johnston et al 2013) and 26 months (CONFIRM trial, Di Leo et al 2014). For sample size calculation, the mOS for fulvestrant in second line is assumed to be 26 months. Based on the expected split of first line and second line patients mentioned above, the median overall survival of control arm is estimated via simulation to be approximately 30 months. It is hypothesized that adding ribociclib to fulvestrant will result in a 29% reduction in the hazard rate for OS

(corresponding to an increase in median survival to 42 months). To detect a hazard ratio of 0.71 with 85% cumulative power, a maximum of 353 deaths need to be observed, (using a log-rank test and a 3-look [superiority only] group sequential design at one-sided cumulative 2.5% level of significance). The sample size calculation was conducted with software package East 6.3.

Based on the number of patients planned to be randomized and 10% dropout rate by the time of OS final analysis, it is estimated that these 353 deaths will be observed at approximately 56 months after the randomization of the first patient. Therefore the estimated time for the final OS evaluation will be 30 months after the primary analysis of the PFS endpoint.

Sample size justification for PK collection

Sparse PK sampling will be performed on approximately 150 patients (Table 7-6). Assuming a 2:1 ratio between the ribociclib and placebo arm, sparse plasma concentrations for ribociclib will be available in approximately 100 patients. Trough PK sampling will be performed in all remaining patients (Table 7-7). PK data collected from this study may also be combined with data from other studies to support a population PK analysis of ribociclib using non-linear mixed effect modeling. The choice of sampling time points was selected to ensure capture of Cmax. The aim of this analysis is to analyze the pharmacokinetics of ribociclib in a sample size as large as possible. This sample is anticipated to represent the covariate distributions in the targeted population. No specific hypothesis will be tested and therefore no specific sample size calculation has been performed. The decisions on number of sparse PK samples and number of patients needed are driven by feasibility.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

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

If there is any question that the patient will not reliably comply, they should not be entered in the 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 anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the

study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1 - Concomitant medications

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

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction and Co-Medication Considerations (v05 release date: 2015), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (qtdrugs.org/).

These lists are not comprehensive and are only meant to be used as a guide. 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	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir , elvitegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Avasimibe[2,3], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]
CYP3A substrates with NTI[1]	Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib, venlafaxine
Herbal preparations/ medications	Herbal preparations/medications 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, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[2] Herbal product
[3] P-gp inducer
[4] Source: qtdrugs.org (as of Apr 7, 2015)
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	Amprenavir, atazanavir, casopitant, cimetidine, darunavir, diltiazem, fosamprenavir, lomitapide, netupitant, tofisopam, verapamil
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, lersivirine, modafinil, nafcillin, talviraline
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, almorexant, aplaviroc, apixaban (doses < 2.5 mg only), atazanavir, aprepitant, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, darifenacin, darunavir, ebastine, eletriptan, eplerenone, felodipine, fluticasone, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, perospirone, quetiapine, ridaforolimus, sildenafil, ticagrelor, tilidine,tolvaptan, triazolam, vardenafil, vicriviroc, voclosporin
Strong BSEP inhibitors	Bosentan, fusidate, glibenclamide, sulindac, troglitazone (TGZ-sulfate)
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, atazanavir, atomoxetine, bedaquiline, clozapine, dexmedetomidine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisertron, iloperidone, isradipine, lithium, mirabegron, mirtazapine, moexipril, norfloxacin, ofloxacin, olanzapine, ondansetron (p.o. only at 4 mg or 8 mg),, oxytocin, paliperidone, pasireotide, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, telavancin, tetrabenazine,tizanidine, tolterodine, vardenafil, ziprasidone
MATE1 and OCT2 substrates[3]	Acyclovir, amantadine, amiloride, cephalexin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), pindolol, procainamide, ranitidine, and varencicline
BCRP substrates	Rosuvastatin, sulfasalazine

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
[2] Source: qtdrugs.org (as of Apr 7, 2015)
[3] Source: FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and implications for Dosing and Labeling (February 2012) and Yonezawa and Inui (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacology 164:1817-25

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

Harmonization of Efficacy Analysis of Solid Tumor Studies

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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

14.2.1 Introduction

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

The efficacy assessments described in Section 14.2.2 and the definition of best response in Section 14.2.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.2.29 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.

14.2.2 Efficacy assessments

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

14.2.3 Definitions

14.2.4 Disease measurability

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

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

For patients without measurable disease see Section 14.2.27.

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.

14.2.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.2.27.

14.2.6 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will

be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

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

techniques can be useful in confirming complete pathological response when biopsies are obtained.

- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.2.7 Baseline documentation of target and non-target lesions

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

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the 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 14.2.4.
- **Nodal target**: See Section 14.2.4.

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

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

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-3) and non-target lesions (Table 14-4) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-5) as well as the presence or absence of new lesions.

14.2.9 Follow-up and recording of lesions

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

14.2.10 Non-nodal lesions

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

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

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

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

14.2.11 Nodal lesions

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

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

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

14.2.12 Determination of target lesion response

Table 14-3 Response criteria for target lesions

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

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 14.2.6.)

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- 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 14-3 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target

lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.

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

lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

14.2.13 Determination of non-target lesion response

Table 14-4 Response criteria for non-target lesions

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

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

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

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK)
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden

has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.2.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.2.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion 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 14.2.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.2.6.

14.2.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-5.

Table 14-5 Overall lesion response at each assessment

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

Target lesions	Non-target lesions	New Lesions	Overall lesion response
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

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

14.2.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.2.27 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.2.17 Best overall response

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

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

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

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

- -For non-randomized trials where response is the primary endpoint, confirmation is needed.
- -For trials intended to support accelerated approval, confirmation is needed

- For all other trials, confirmation of response may be considered optional.

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

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

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

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

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

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

measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

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

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

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

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

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

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

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

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

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

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

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

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

be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.2.18 Time to event variables

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

14.2.19 Progression-free survival

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

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

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

14.2.20 Overall survival

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

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

14.2.21 Time to progression

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

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

14.2.22 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.

[redacted]

14.2.24 Duration of response

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

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

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

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

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

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

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

14.2.25 Time to response

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

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.2.24. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

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

Assessment date

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

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

Start dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.2.27).

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

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is

used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-6.

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

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

[1] As defined in Section 14.2.8.

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

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

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

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

14.2.28 Sensitivity analyses

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

Based on definitions outlined in Section 14.2.26, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-7 Options for event dates used in PFS, TTP, duration of response

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

[1].=Definitions can be found in Section 14.2.26
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.26.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

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

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

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

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

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

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

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

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-7 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

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

14.2.29 Data handling and programming rules

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

14.2.30 Study/project specific decisions

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

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

14.2.31 End of treatment phase completion

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

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation

- Technical problems
- Subject/guardian decision
- 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)

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

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

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

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

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

14.2.33 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the

programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

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

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

14.2.34 Programming rules

The following should be used for programming of efficacy results:

14.2.35 Calculation of 'time to event' variables

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

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

14.2.36 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.2.26). If all measurement dates have no day recorded, the 1st of the month is used.

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

14.2.37 Incomplete dates for last known date patient alive or death

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

14.2.38 Non-target lesion response

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

14.2.39 Study/project specific programming

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

14.2.40 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-7)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.2.26. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

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

14.2.41 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

EMA Guidance: 2012 Guideline on the evaluation of anticancer medicinal products in man

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

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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 - Bone Marrow Reserve in Adults

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

MARROW DISTRIBUTION OF THE ADULT

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

14.4 Appendix 4 - Patient reported outcomes

Figure 14-1 EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

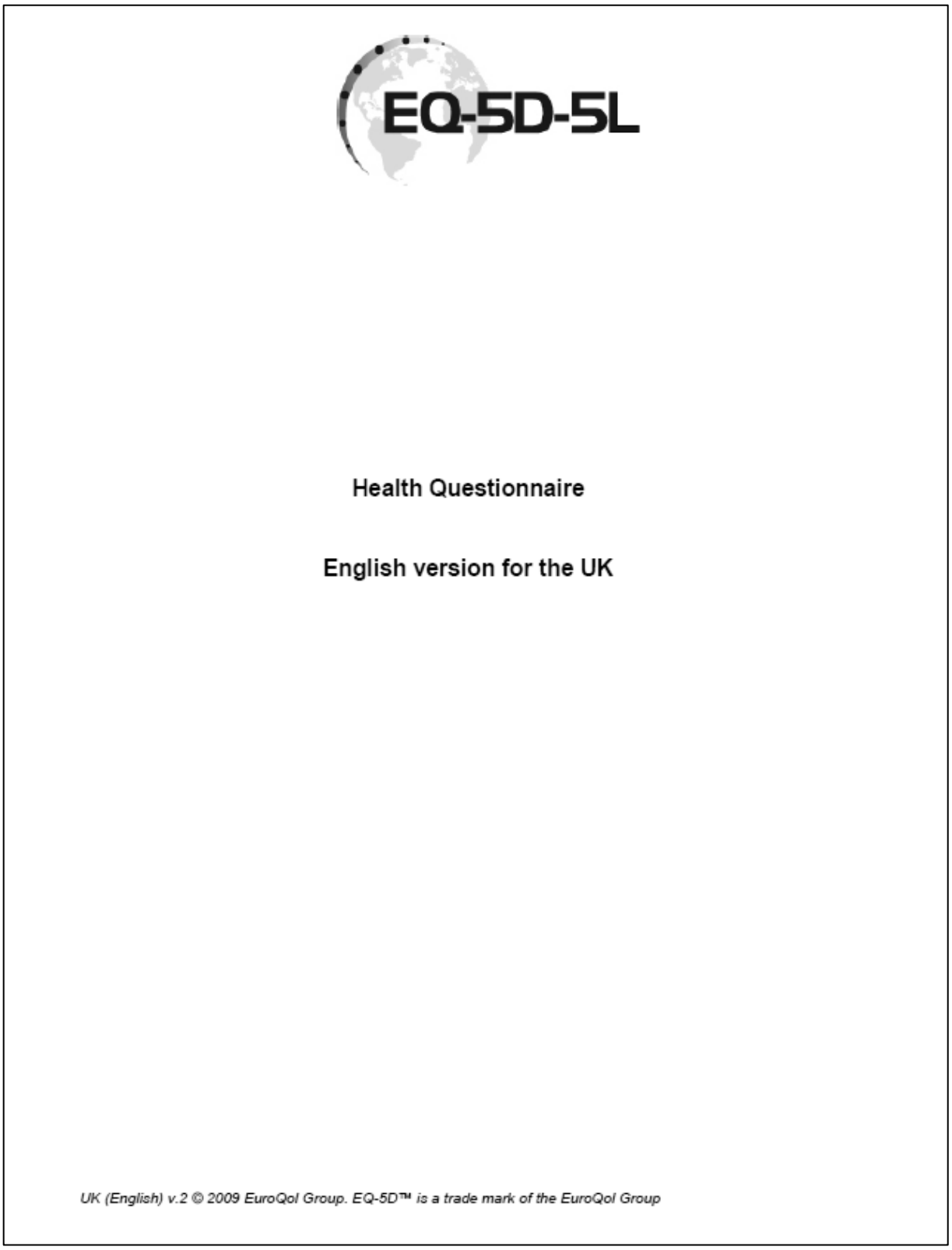
29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Figure 14-2 EQ-5D-5L



Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

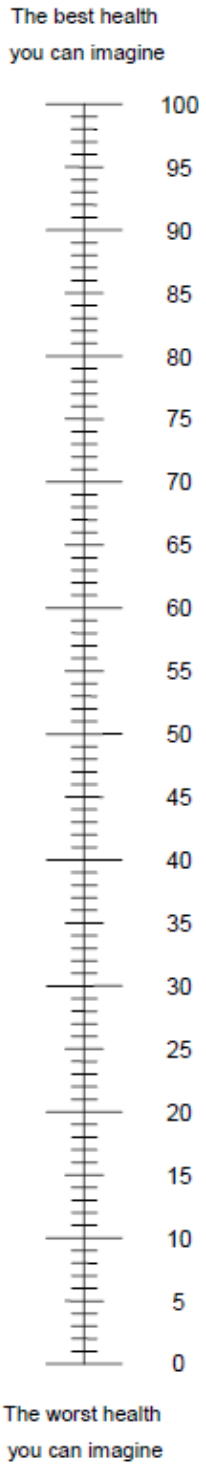


Figure 14-3 Brief Pain Inventory-Short Form

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

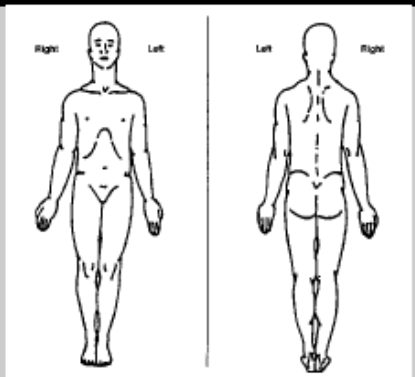
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes