NOVARTIS

Clinical Development

Ribociclib (LEE011)

Oncology Clinical Protocol CLEE011G2301 (EarLEE-1) / NCT03078751

An open label, multi-center protocol for U.S. patients enrolled in a study of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, high risk early breast cancer

Authors [redacted]

Document type	Amended Protocol Version
EUDRACT number	2014-001795-53
Version number	02 (Clean)
Development phase	II
Document status	Final
Release date	17-Apr-2018

Template version 22-Jul-2016

Table of contents

Table of contents 2
List of tables 5
List of abbreviations 6
Glossary of terms 9
Protocol summary 10
Amendment 2 (17-Apr-2018) 14
Amendment 1 (21-Jun-2017) 17
1 Background 19
1.1 Overview of disease pathogenesis, epidemiology and current treatment 19
1.1.1 Epidemiology 19
1.1.2 Treatment of EBC 19
1.1.3 Role of the CDK4/6 pathway in BC 21
1.2 Introduction to investigational treatments and other study treatments 22
1.2.1 Overview of ribociclib 22
1.2.2 Overview of adjuvant endocrine therapy 25
2 Rationale 27
2.1 Study rationale and purpose 27
2.2 Rationale for the study design 28
2.3 Rationale for dose and regimen selection 30
2.4 Rationale for choice of combination drugs 30
2.5 Rationale for choice of comparators drugs 30
2.6 Risks and benefits 30
3 Objectives and endpoints 31
4 Study design 31
4.1 Description of study design 31
4.1.1 Screening phase 32
4.1.2 Treatment phase 32
4.1.3 Follow up phase 33
4.2 Definition of end of study 33
4.3 Early study termination 34
5 Population 34
5.1 Patient population 34
5.2 Inclusion criteria 34
5.3 Exclusion criteria 37
6 Treatment 39

6.1 Study treatment 39
6.1.1 Dosing regimen 40
6.1.2 Guidelines for continuation of treatment 42
6.1.3 Study treatment duration 42
6.2 Dose modifications 42
6.2.1 Dose modification and dose delay 42
6.2.2 Follow-up for toxicities 46
6.3 Concomitant medications 48
6.3.1 Permitted concomitant therapy 48
6.3.2 Permitted concomitant therapy requiring caution 49
6.3.3 Prohibited concomitant therapy 50
6.3.4 Other procedures 51
6.4 Patient numbering, treatment assignment or randomization 51
6.4.1 Patient numbering 51
6.4.2 Treatment assignment or randomization 51
6.4.3 Treatment blinding 52
6.5 Study drug preparation and dispensation 52
6.5.1 Study treatment packaging and labeling 52
6.5.2 Drug supply and storage 53
6.5.3 Study drug compliance and accountability 53
6.5.4 Disposal and destruction 54
7 Visit schedule and assessments 54
7.1 Study flow and visit schedule 54
7.1.1 Screening 59
7.1.2 Treatment period 61
7.1.3 Discontinuation of study treatment 61
7.1.4 Follow up for safety evaluations 63
7.1.5 Follow-up phase 63
7.1.6 Lost to follow-up 63
7.2 Assessment types 63
7.2.1 Recurrence assessments 63
7.2.2 Safety and tolerability assessments 64
7.2.3 Biomarkers 68
7.2.4 Resource utilization 68
7.2.5 Patient reported outcomes 68
8 Safety monitoring and reporting 68

8.1 Adverse events 68
8.1.1 Definitions and reporting 68
8.1.2 Laboratory test abnormalities 70
8.1.3 Adverse events of special interest 70
8.2 Serious adverse events 70
8.2.1 Definitions 70
8.2.2 Reporting 71
8.3 Emergency unblinding of treatment assignment 71
8.4 Pregnancies 72
8.5 Warnings and precautions 72
8.6 Data Monitoring Committee 72
8.7 Steering Committee 72
9 Data collection and management 72
9.1 Data confidentiality 72
9.2 Site monitoring 73
9.3 Data collection 73
9.4 Database management and quality control 74
10 Statistical methods and data analysis 75
10.1 Interim analysis 75
10.2 Sample size calculation 75
11 Ethical considerations and administrative procedures 75
11.1 Regulatory and ethical compliance 75
11.2 Responsibilities of the investigator and IRB/IEC/REB 75
11.3 Informed consent procedures 76
11.4 Discontinuation of the study 76
11.5 Publication of study protocol and results 76
11.6 Study documentation, record keeping and retention of documents 77
11.7 Confidentiality of study documents and patient records 78
11.8 Audits and inspections 78
11.9 Financial disclosures 78
12 Protocol adherence 78
12.1 Amendments to the protocol 78
13 References (available upon request) 80
14 Appendices 84
14.1 Appendix 1: Guidelines for Anatomic and Prognostic Stage Group III of HR-positive, HER2-negative Breast Cancer for breast cancer staging (based on AJCC Ed. 8th) 84

14.2 Appendix 2: Concomitant medications 86

List of tables

Table 3-1 Objectives and related endpoints 31
Table 6-1 Dose and treatment schedule 40
Table 6-2 Dose modification guidelines 42
Table 6-3 Ribociclib dose adjustment and management recommendations for hematological adverse reactions 43
Table 6-4 Ribociclib dose adjustment and management recommendation for hepatic toxicities 44
Table 6-5 Ribociclib dose adjustment and management recommendation for QTcF prolongation 45
Table 6-6 Ribociclib dose adjustment and management recommendation for all other adverse reactions 46
Table 6-7 Packaging and labeling 53
Table 6-8 Supply and storage of study treatments 53
Table 7-1 Visit evaluation schedule 55
Table 7-2 Clinical laboratory parameters collection plan (all are done locally with the protocol amendment 02) 65
Table 7-3 Local clinical laboratory parameters assessment plan 67
Table 7-4 ECG collection plan (all ECGs are performed and assessed locally with the protocol amendment 02) 67
Table 14-1 AJCC 8th edition Anatomic Stage Groups (not including Group IV - all M-category M0) 84
Table 14-2 AJCC 8th edition Prognostic Stage Group III of HR-positive, HER2-negative Breast Cancer (all M-category M0) 84
Table 14-3 List of prohibited medications during study drug treatment 86
Table 14-4 List of medications to be used with caution during study drug treatment 87

List of abbreviations

AE	Adverse Event
AESI	Adverse events of special interest
AI	Aromatase inhibitor
AJCC	American Joint Committee on Cancer
ALND	Axillary lymph node dissection
ALP	Alkaline Phosphatases
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolutely Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BC	Breast cancer
BCRP	Breast cancer resistance protein
BSEP	Bile salt export pump
BUN	Blood Urea Nitrogen
CABG	coronary artery bypass graft
CAP	College of American Pathologists
CCND1	Cyclin D1
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
Cmax	Maximum Concentration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CV	Coefficient of variation
CYP	Cytochrome P450
DDFS	Distant disease free survival
DDI	Drug-Drug Interaction
DHEA	dehydroepiandrosterone
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic Acid
DS&E	Drug Safety and Epidemiology
DSS	Disease-specific survival
EBC	Early Breast Cancer
EBCTCG	EBC Trialists' Collaborative Group
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
ER	Estrogen receptor
ET	Endocrine Therapy
FISH	Fluorescence in situ hybridization
FMO3	flavin-containing monooxygenase 3
FSH	Follicle-stimulating hormone
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone
HADS	Hospital Anxiety and Depression Scale
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HER2 -	Human epidermal growth factor receptor 2 negative
HR	Hormone Receptor
HR positive	Hormone Receptor positive
HSV	Herpes Simplex Virus
i.v.	intravenous(ly)
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iDFS	Invasive disease-free survival
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LRRFS	Loco-regional recurrence-free survival
LVEF	Left Ventricular Ejection Fraction
MATE1	multidrug and toxin extrusion protein-1
MI	Myocardial infection
MRI	Magnetic Resonance Imaging
MUGA	Multiple Gated acquisition
NaF-PET	Sodium fluoride positron emission tomography
NASH	Non-alcoholic fatty liver disease
NCI	National Cancer Institute
OCT2	Organic cation transporter 2
OS	Overall survival
p.o.	per os/by mouth/orally
PFS	Progression-free survival
P-gp	P-glycoprotein

PgR	Progesterone Receptor
PHI	Protected Health Information
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PT	Prothrombin time
PVCs	Premature ventricular contractions
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
Rb	Retinoblastoma protein
RBC	Red Blood Cells
REB	Research Ethics Board
RFS	Recurrence free survival
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SEER	Surveillance, Epidemiology, and End Results Program
SISH	Silver in situ Hybridization
SLN	Sentinel lymph node
SOP	Standard Operating Procedure
TBIL	Total Bilirubin
TdP	Torsades de Pointe
Tmax	The time at which the maximum observed concentration (Cmax) occurs
ULN	Upper Limit of Normal
WBC	White blood cell count

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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: 28 days)
Dose level	The dose of drug given to the patient (e.g. total daily)
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 USA Code of Federal Regulations (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 (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Phase	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, treatment, follow up
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm/group 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 patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination.
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

Protocol summary

Title	An open label, multi-center protocol for U.S. patients enrolled in a study of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, high risk early breast cancer
Brief title	A protocol for U.S. patients enrolled in a study of ribociclib with endocrine therapy in patients with hormone receptor-positive, HER2-negative, high risk early breast cancer.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	While adjuvant endocrine therapy (ET) is effective in reducing risk of recurrence in patients with hormone receptor (HR)-positive early breast cancer (EBC), recurrences are still common, especially in patients with unfavorable clinical, pathological and/or molecular features. Ribociclib, a CDK4/6 inhibitor, demonstrated clinical efficacy with tolerable toxicity when added to ET in patients with HR-positive, HER2-negative advanced breast cancer. The purpose of this study is to collect the safety data on the combination of ribociclib + ET in HR+, HER2-negative high–risk EBC patients who enrolled in this study prior to the early closure of enrollment on 12 Feb 2018.Patients were randomized in the US only. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen) for 26 cycles of ribociclib.
Primary Objective(s) and Key Secondary Objective	**Primary:** The main objective of the study is to evaluate the preliminary safety and tolerability of the ribociclib + ET in patients that were randomized to ribociclib + ET prior to the early closure of enrollment. **Key secondary**: none
Secondary Objectives	None
Study design	This was a randomized, phase III, double-blind, placebo-controlled, multi-center, international study to evaluate efficacy and safety of ribociclib with ET as an adjuvant treatment in patients with HR-positive, HER2-negative high risk EBC. Following the early closure of enrollment and the protocol amendment 02, the study will change to a phase II study conducted in the US only. It will include: ● Screening phase where written informed consent will be collected and all eligibility criteria verified (28 days) – this phase has been completed for all patients as of 12 February 2018; ● Treatment phase: Ribociclib patients were randomizedreceive ribociclib 600 mg once daily on days 1 to 21 of a 28 day cycle or placebo in combination with standard adjuvant ET. With the early closure of enrollment, all patients were unblinded. Patients randomized to placebo + ET permanently discontinued study treatment after unblinding. After unblinding, patients randomized to ribociclib will receive ribociclib + ET treatment for a maximum of 26 cycles (approximately 24 months) or until first disease recurrence, intolerable toxicity, withdrawal of consent, death or discontinuation from the study treatment for any other reason, whichever is earlier ET may start up to 12 weeks before the date of randomization. ET includes orally administered, letrozole, anastrozole, or exemestane. In premenopausal women the ET will include GnRH agonists (such as goserelin, triptorelin or leuprolide.) **(**Tamoxifen is not permitted as an ET combination partner as of 17 Feb 2018). ET should not be changed during treatment with ribociclib unless intolerable toxicity, patient's request, or any other medically-important event that requires change of ET. Patients will have safety and recurrence assessments while on ribociclib therapy

	as per protocol. All patients, regardless of the reason for treatment discontinuation (except death) will be followed for safety for 30 days after the last dose of ribociclib ● Follow up phase With the protocol amendment 02, follow-up phase assessments are no longer performed. ● For each patient randomized to placebo + ET, study participation will end following the safety follow-up after the last dose of placebo. ● For each patient randomized to ribociclib + ET, study participation will end following the safety follow up after the last dose of ribociclib. ● Patients who are during their follow-up phase assessments at the time of the protocol amendment 02 will end study participation. The study will end when all patients have discontinued ribociclib treatment and have undergone the safety follow-up 30 days after the end of treatment (EOT). The study is expected to continue for approximately 25 months after the last patient randomized to ribociclib completed an end of treatment safety follow-up.
Population	The study will include pre- and postmenopausal women with HR-positive, HER2-negative high risk EBC after adequate surgical resection, radiotherapy (if indicated), adjuvant or neo-adjuvant chemotherapy, and who are deemed to be eligible for adjuvant ET for at least 60 months of duration. 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.
Key Inclusion criteria	No changes were made to the eligibility criteria since all patients were randomized prior to the closure of enrollment and the release of the protocol amendment 02. ● Patient is a female with known menopausal status at the time of initiation of adjuvant ET or male adult ≥18 years-old at the time of informed consent ● Patient with histologically confirmed unilateral primary invasive adenocarcinoma of the breast ● Patient has breast cancer that is positive for estrogen-receptor and/or progesterone-receptor (determined on the most recently analyzed tissue sample and tested by a local laboratory based on the ASCO-CAP Guidelines (Hammond et al 2010)) ● Patient has HER2-negative breast cancer by local laboratory testing ● Patient has available archival tumor tissue from the surgical specimen ● Patient after surgical resection where tumor was removed completely, with the final surgical specimen microscopic margins free from tumor, and: ● Patients who received adjuvant chemotherapy and have tumor characteristics as defined in the AJCC 8th edition Prognostic Stage Group III **Note:** Categorization into AJCC 8th edition Prognostic Stage Group III requires determination of the T- and N-categories, grade of the tumor and ER and PR status. Axillary lymph node dissection (ALND) is a preferred method for axillary lymph node staging, however sentinel lymph node (SLN) dissection can be used to determine the N-category as follows: ● no metastasis in SLN - patient is considered as having N-category N0, ● at least one tumor metastasis larger than 2.0 mm in 1-2 SLNs in a patient with no clinically-detectable lymph nodes, T1-2 tumors, and no gross extra-nodal tumor extension - patient is considered as having N-category N1 (This category of selected patients with metastatic SLN and no ALND will be limited to no more than 20% of the accrual total), ● ALND is required to determine the N-category and Prognostic Stage Group in all other patients, **or** ● Patients who received neoadjuvant chemotherapy and have 1 or more ipsilateral axillary lymph nodes with residual tumor metastases greater than 2.0 mm in lymph node(-s) and residual tumor greater than 10.0 mm in breast tissue surgical specimen

	● Patient has completed multi-agent adjuvant or neoadjuvant chemotherapy of ≥ 4 cycles or ≥ 12 weeks in duration which included taxanes in the regimen ● Patient has completed adjuvant radiotherapy (if indicated) according to the institutional guidelines prior to screening ● Patient has no contraindication for the adjuvant ET and is planned to be treated by ET for 5 years or more ● Patient may already have initiated ET at the time of randomization, but randomization must take place within 52 weeks of date of initial histological diagnosis of breast cancer and within 12 weeks of initiating standard adjuvant ET. Ovarian suppression for fertility preservation is not considered adjuvant ET ● Patient has an Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 ● Patient has adequate bone marrow and organ function per pre-defined criteria as assessed by the central lab ● Patient has, sodium, potassium, phosphorus, magnesium and total calcium laboratory values within normal limits ● QTcF interval (using Fridericia's correction) < 450 msec and mean resting heart rate 50-90 bpm Please refer to Section 5.2 for the complete list and all specific details on Inclusion Criteria.
Key Exclusion criteria	● Patient has received any CDK4/6 inhibitor ● Patient has received prior treatment with tamoxifen, raloxifene or aromatase inhibitors for reduction in risk (chemoprevention) of breast cancer and/or treatment for osteoporosis within last 2 years prior to screening ● Patient has received prior treatment with anthracyclines at cumulative doses of 450 mg/m² or more for doxorubicin or 900 mg/m² or more for epirubicin ● Patient with distant metastases of breast cancer beyond regional lymph nodes ● Patient has not recovered from clinical and laboratory acute toxicities of chemotherapy, radiotherapy and surgery (i.e., patient has adverse events attributed to prior anti-neoplastic therapy NCI CTCAE version 4.03 grade ≥1 at day of enrollment, excluding alopecia and amenorrhea) ● Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality (per defined criteria) ● Clinically significant cardiac arrhythmias ● Uncontrolled hypertension with systolic Blood Pressure >160 mmHg ● Patient is currently receiving any of the following prohibited substances and cannot be discontinued 7 days prior to Cycle 1 Day 1: concomitant medications, herbal supplements, and/or fruits and their juices that are known as strong inhibitors or inducers of CYP3A4/5; medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5; systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment; concomitant medications with a known risk to prolong the QT interval and/or known to cause Torsades de Pointes that cannot be discontinued or replaced by safe alternative medication. ● Patient has any concurrent severe and/or uncontrolled medical condition that would, in the investigators judgment cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol, or limit life expectancy to ≤5 years ● Pregnant or breast-feeding (lactating) women or women who plan to become pregnant or breast-feed during the study ● Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study treatment and for 21 days after stopping the study treatment. Please refer to Section 5.3 for the complete list and all specific details on Exclusion Criteria.
Investigational and reference therapy	During Treatment phase ribociclib will be given orally once a day on days 1-21 of each 28 day cycle. Days 22-28 of each cycle will be a "rest" period from ribociclib.

	Endocrine therapy (ET) will be given orally once a day on a continuous daily schedule (e.g., days 1-28 of each 28-day cycle). GnRH agonist (examples include but not limited to goserelin, triptorelin or leuprolide) will be given every 4 weeks for pre-menopausal women only. There will be no “rest” period in the ET schedule. The study drugs will be administered as a flat-fixed dose, and not by body weight or body surface area. All oral study treatment drugs must be administered together at approximately the same time each day and can be given with or without food. Evening or night doses are strongly not recommended.
Recurrence assessments	Recurrence (including local, regional, or distant, or contralateral invasive breast cancer, or second primary non-breast invasive cancer) will be assessed by investigator according to local or institutional standards of care, as clinically indicated, or at any time when recurrence is suspected. Suspicion of recurrence during clinical evaluation may be evaluated by CT or MRI, bone scan, ultrasound, PET, plain X-ray films, or mammography, and maybe confirmed by histological (or cytological, when applicable) examination.
Safety assessments	● Physical examinations ● Height, weight, and vital signs ● 12 lead ECGs ● Laboratory assessments including hematology, biochemistry, coagulation, pregnancy tests (for women of childbearing potential) and urinalysis ● All adverse events (AEs) will be reported until end of the 30-days safety follow up
Other assessments	Starting with the protocol amendment 02, tissue and blood samples collection, collection of patient questionnaires, and reporting of data regarding hospitalizations will no longer be collected.
Data analysis	The final data summaries will be reported after all patients discontinue ribociclib and complete the safety follow-up assessment 30 days after the last dose of ribociclib. All key baseline and safety data will be summarized. Additional listings may be provided to summarize efficacy data collected.
Key words	hormone receptor-positive, HER2-negative, high risk early breast cancer, adjuvant, ribociclib, endocrine therapy, CDK4/6, Phase II, estrogen receptor-positive, progesterone receptor-positive

Amendment 2 (17-Apr-2018)

Study CLEE011G2301 was initiated on June 20, 2017. On 19 January 2018, a planned safety review by the independent Data Monitoring Committee was performed and no safety concerns were identified.

The study had an early enrollment closure on 12 February, 2018; the decision to close enrollment was not based on safety concerns. As of 12 February 2018, 54 female patients were randomized at sites in the United States (U.S.) only. All randomized patients were unblinded; patients randomized to the placebo arm permanently discontinued the study after the safety follow-up assessment and patients randomized to the ribociclib arm were offered the opportunity to continue investigational treatment with ribociclib + ET for a maximum of 26 cycles. The decision to continue ribociclib was left to investigator and patient discretion.

Amendment Rationale

1. The study was closed to enrollment early. The main purpose of this amendment is to evaluate the preliminary safety and tolerability of the ribociclib + ET in patients that were randomized to ribociclib + ET prior to the early closure of enrollment, and to allow patients randomized to ribociclib + ET to continue treatment for a maximum of 26 cycles if desired, based upon investigator and patient decision. Patients were randomized in the U.S. only.
2. In another Novartis study CLEE011E2301 (MONALEESA-7) an imbalance in the QT prolongation was observed in the subgroup of patients receiving tamoxifen versus non-steroidal aromatase inhibitors in combination with ribociclib while the overall safety profile was comparable. Specifically, a greater than expected QT prolongation was observed in the tamoxifen with placebo group (Tripathy et al 2017). Novartis is continuing to analyze the MONALEESA-7 study results to better understand the efficacy and safety data of combination of tamoxifen and ribociclib. However, due to availability of alternative therapies to tamoxifen in the EarLEE-1 protocol (i.e. letrozole, anastrozole, or exemestane), tamoxifen is not permitted to be used in combination with ribociclib in this study.
   As of 12 February 2018, there were no patients in the study on treatment by combination of tamoxifen and ribociclib.
3. Changes were introduced to the ribociclib dose adjustment and management recommendations in Table 6-5 to mitigate the risk of subsequent QTcF prolongation in patients who experienced QTcF prolongation > 480 msec.
4. Recurrence is assessed periodically by investigator as clinically indicated, or at any time when recurrence is suspected according to local or institutional standard of care.
5. The lists of prohibited medications and medications to be used with caution during study drug treatment were updated, along with other updates.

Changes to the protocol

Section 1.2, Section 1.2.2.1, Section 2.4, Section 2.5, Section 4.1.2, Section 6.1.1, Table 6.1, Section 6.3.4, Section 6.5, Table 6.7 and Table 6.8 are revised to remove tamoxifen.

Section 1.2.2 Update with a new clinical data from [CLEE011E2301] (MONALEESA-7) study related to tamoxifen.

Section 2.1, Section 2.2, Section 5.1, Section 6.4.1, Section 6.4.2 and Section 7.1 are revised as the enrolment is early terminated.

Section 2.6, Table 3.1, Section 4.2, Section 6.4.3 and Section 8.3, are revised as the enrolment is early terminated and the patients have been unblinded.

Section 2.2, Section 2.4, Section 2.5, Section 4.1, Section 6.1.1 and section 6.4.2 are revised to remove the men as no man has been enrolled at the time of the enrolment termination.

Section 4.1, Section 4.1.2, Section 4.1.3, Section 4.3, Section 6.1.1, Section 6.1.2, Table 7.1, Section 7.1.2 and Section 7.1.5 are revised as the unblinded patients will continue on ribociclib + ET arm till end of treatment (26 cycles maximum) and the patient under placebo discontinued the study. The follow up phase is removed.

Table 3-1, Section 4, Section 6, Section 7 and Section 9 are revised as placebo is removed.

Figure 4-1 has been removed as only patients randomized to ribocilib are in the treatment phase and the follow up phase is not applicable anymore.

Section 4.1.2, Section 6.4.1 and Table 7-1 are revised to remove the use of IRT system at randomization as no longer applicable.

Section 4.1.2, Section 6.1.1, Table 7-1, Section 7.1.3, Section 7.2.1, Table 7-2, Table 7-3, Appendix 2 and Appendix 3 are revised as the recurrence is assessed periodically by investigator as clinically indicated and no longer be assessed according to the STEEP System.

Section 4.1.3.1 is revised as the follow up phase is no longer applicable.

Section 4.3 is revised as the patients have been unblinded and will continue in the study, and may have an option to be enrolled in a separate protocol, if applicable, by end of treatment of the current study. In addition, the maximal duration of the study has been updated.

Section 6.1 and Table 6.8 are revised as ET will be supplied locally.

Table 6.5 is revised for updating Ribociclib/placebo dose adjustment and management recommendation for QTcF prolongation.

Section 7.1.1, Table 7-1, Section 7.2.2 and Section 7.2.2.4 are revised to remove the performance status (ECOG).

Table 7-4 is removed as the performance status (ECOG) is no longer applicable in the study.

Section 7.2.1 is revised to specify that the recurrence will be assessed by investigator according to local or institutional standards of care, as clinically indicated, or at any time when recurrence is suspected.

Section 7.2.2, Section 7.2.5 and Table 7.1 are revised to remove Patient Reported Outcomes that are no longer applicable in the study.

Table 7.9 is removed as PRO assessments are no longer applicable in the study.

Section 7.2.2.5 and Table 7.5 are revised as all the laboratory assessments will be performed locally, and not centrally anymore.

Section 7.2.2.6 and Table 7.7 are revised as all the ECGs assessments will be performed locally, and not centrally anymore.

Section 6.2.1.2, Table 7-1, Section 7.2.2.6.1 and Table 7-7 are revised to change triplicate to single ECGs.

Section 7.2.3, Table 7.1 and Section 11.3 are revised to remove Biomarkers that are no longer applicable in the study.

Table 7-8 is removed as Biomarkers are no longer applicable in the study.

Section 7.2.4 and Table 7.1 are revised as collection of data for healthcare resource utilization is no longer performed.

Section 8.6 and Section 8.7 are revised to remove Data monitoring Committee and Steering Committee that are no longer applicable in the study.

Section 9.3 and Section 9.4 are updated as PRO and Biomarkers data will not be collected anymore in the eCRF.

Section 10 is revised as the data analysis for this study will be limited to key summaries of safety and baseline characteristics. The final analysis will be performed after all patients have discontinued the study treatment and the safety follow-up.

Appendix 4, Table 14-4 is revised to remove the strong CYP2D6 inhibitors or inducers (for patients receiving tamoxifen) and to update the Medications List with a known risk for QT prolongation.

Appendix 4, Table 14-5 is revised to remove the strong CYP2C9 substrates with NTI (for patients receiving tamoxifen) and to update the Medications List with possible risk for QT prolongation.

Appendix 5 is removed as PRO assessments are no longer applicable in the study.

IRBs/IECs

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

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.

Amendment 1 (21-Jun-2017)

Study CLEE011G2301 was initiated on June 20, 2017.

Amendment Rationale

The main purpose of this amendment is to address the recommendation from the Health Authorities to exclude patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or soy allergy due to excipients of placebo tablets. In addition, minor clarifications to inclusion criterion, study assessments and procedures were provided as described below.

Changes to the protocol

- Section 4.1.2 and 6.1.1: Clarification was added that when investigators change ET in the event of intolerable toxicity, patient's request, or any other medically important event that required change of ET, there is no need to notify Novartis medical monitor.
- Section 5.2 and Protocol Summary: Inclusion criteria 7 was updated to clarify that patients are eligible after surgical resection where tumor was removed completely with the final surgical specimen microscopic tumor margins free from tumor.
- Section 5.3: Exclusion criteria 4 was updated to clarify that patients with a known hypersensitivity to any of the excipients of placebo (e.g. rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or soy allergy) will not be eligible for the study.
- Section 6.1 and 6.5.2 (Table 6-8): It was clarified that ET will be sourced locally or will be supplied by Novartis or its designee according to local practices and regulations in each participating country.
- Table 7.1: To address inconsistency between Table 7-1 and Table 7-7, clarification was provided to Table 7-1 that the ECG assessment is performed at Cycle 7 Day 1 in all patients.
- Section 7.2.2.6: Clarification was added that the ECG assessment should be performed at least 3 business days prior to the scheduled randomization date to ensure ECG evaluation is received from central laboratory in time for eligibility assessment. Also, patient initials will not be collected on ECG tracings.
- Section 7.2.3.3.1 and Protocol Summary: Clarification was provided to the Pharmacogenetics Assessments section that genome-wide association studies (GWAS) will include exploration of inherited genetic factors such as CYP3A4 (e.g. CYP3A4 polymorphism) that may affect the response (both adverse [e.g. neutropenia] and therapeutic effects) to treatment.
- Section 7.2.4: Clarification was added to address the inconsistency between Table 7-1 and Section 7.2.4 that healthcare resource utilization data regarding hospitalizations should be captured throughout the study treatment phase and post treatment follow up phase.

- Section 10.6.2.3.2: Clarification was added that any additional exploratory analysis on biomarkers (e.g. CYP3A4 polymorphism) will be detailed in SAP.
- Section 14.4: List of prohibited medications during study treatment was updated as follows; venlafaxine was moved from medications with a known risk for QT prolongation category to medications that carry a possible risk for QT prolongation. Loperamide was added to the medications that carry a possible risk for QT prolongation.

IRBs/IECs

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

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

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

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Epidemiology

Breast cancer (BC) is the most frequently diagnosed cancer worldwide. Approximately 1.7 million new cases of BC and 522,000 deaths attributed to BC were estimated to occur in 2012 worldwide (Torre et al 2012). BC incidence varies between individuals of different ethnicities and in different geographic locations around the world with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 92 in Northern America (GLOBOCAN 2012). In the United States, BC was projected to be the most common cancer diagnosed in 2016 with an estimated incidence of 249,260 new cases and 40,890 deaths attributed to BC (Siegel et al 2016). Estimated incidence of BC in European countries in 2012 was 458,337 (Ferlay et al 2013). BC in men is not common with a reported frequency of approximately 1% of all BC, but the incidence of this disease in men is continuously rising (Eggeman et al 2013).

The vast majority of newly diagnosed BC cases are early breast cancers (EBC) localized to the breast tissue and regional lymphatics and which are potentially curable with locoregional treatment modalities, such as surgery and radiation therapy. Based on Surveillance, Epidemiology, and End Results Program (SEER) data collected between years 1975 and 2012, 93% of cases of BC diagnosed were EBC, with 61% limited to the breast tissue and 32% localized within the breast tissue and regional lymph nodes (Howlander et al 2015).

1.1.2 Treatment of EBC

Besides primary surgery, management of EBC usually includes additional anti-neoplastic treatment modalities such as radiation therapy and adjuvant or neoadjuvant systemic therapy. Although many patients with EBC may be rendered disease-free with surgical resection and radiotherapy, distant recurrence due to not clinically evident at presentation ("micro-metastatic") disease is common and is the primary cause of death in patients with EBC (Anampa et al 2015). According to the EBC Trialists' Collaborative Group (EBCTCG) meta-analysis of almost 150,000 women in 200 randomized clinical trials, approximately 36% and 20% of patients with EBC without any adjuvant systemic therapy will experience recurrence and death due to BC, respectively, during 5 years of follow up (EBCTCG 2005). Moreover, recurrences and BC-related deaths in patients with hormone receptor (HR)-positive EBC continue to occur after 5 years from surgery, with only 45% of patients reported to be recurrence-free at 15 years of follow-up.

Adjuvant systemic treatments that comprise cytotoxic, biological and endocrine therapies in patients with EBC decrease locoregional and distant recurrences, decrease BC-specific mortality and improve overall survival (EBCTCG 2005). The need and selection of systemic adjuvant therapies is based on individual risk of recurrence and is guided by several clinical, pathological and genomic predictive and prognostic factors of tumor and patient such as tumor stage, histopathological grade, tumor HR content, human epidermal growth factor receptor-2 (HER2) amplification status, multi-gene testing recurrence scores, menopausal

status, patient's comorbidities, age, and others. Using these factors, EBC can be classified as having low, intermediate/moderate or high risk for recurrence after surgery (Anampa et al 2015). While there is no consensus on definition of these risk groups, generally, patients with smaller tumors, no metastasis in regional lymph nodes, low tumor grade, HR-positive and HER2-negative status, and low recurrence genomic score have also low risk of recurrence (i.e., 5-10% recurrences at 5-years). These patients are usually considered for adjuvant endocrine treatment, without chemotherapy, due to a lower clinical benefit of latter versus the former. On the other hand, patients with metastases in multiple regional lymph nodes, high tumor grade, HER2-positive status or high recurrence genomic score have a higher risk of recurrence if not treated. These patients are usually considered for adjuvant chemotherapy (HER2 targeting agents are offered to patients with HER2-positive BC), and if the tumor expressed HR, endocrine adjuvant therapy is considered too (usually delivered after the completion of chemotherapy). Complexity and importance of risk definition in EBC reflected in the recent 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging System for patients with breast cancer (Hortobagyi et al 2017). This Staging System included pathological features (i.e. histopathological grade) and biomarkers status (hormone receptors and HER2) in addition to anatomic spread of the tumor (i.e. specific T-, N- and M-categories) to define prognostic stage groups that have similar treatment approaches and prognosis (survival) of patients treated with current standard multimodality treatment (Amin 2016).

Chemotherapy to reduce recurrence risk can be administered preoperatively too. While no significant difference in long-term outcomes between adjuvant and neoadjuvant chemotherapy was found, neoadjuvant chemotherapy increases rates of breast conservation by downsizing large tumors and may provide important prognostic information based on response to the therapy (Mauri et al 2005). For example, extent of residual disease after neoadjuvant chemotherapy correlates with disease-specific survival (DSS) when patients with less than complete pathological response tend to have a higher disease-specific mortality and patients with residual disease in lymph nodes had poorer outcomes than patients with residual disease in the breast tissue only (Jeruss et al 2008).

It is estimated that 75% of BC express receptors for steroid hormones (estrogen and/or progesterone) (Hammond et al 2010), and therefore may benefit from endocrine therapy with tamoxifen or aromatase inhibitors (AIs) (letrozole, anastrozole or exemestane). Endocrine therapy (ET), independent of chemotherapy, reduces the risk of recurrence and BC deaths in HR-positive EBC (EBCTCG 2005). Current clinical guidelines for adjuvant ET in the HR-positive EBC recommend for premenopausal women use of (1) 5-10 years of tamoxifen with or without ovarian suppression (ovarian suppression is recommended for women with high risk for recurrence after adjuvant chemotherapy), or (2) 5 years of AI with ovarian suppression. Clinical guidelines and expert opinions recommend for postmenopausal women, either (1) initial AI for 5 years (or up to 10 years, based on recently reported results of MA.17R, a randomized clinical trial of extending adjuvant letrozole for 5 years after completing initial 5 years (Goss et al 2016)), or (2) initial tamoxifen for 2-3 years followed by AI either to up to total 5 years, or up to 5 years of treatment with AI, or (3) tamoxifen for ~5 years followed by 5 years of AI, or (4) tamoxifen up to 10 years (Gradishar et al 2016; Senkus et al 2016). Limited data on EBC in men suggest that tamoxifen without gonadotropin-releasing hormone (GnRH) agonist should be the ET of choice for HR-positive, HER2-negative EBC (Fentiman et al 2006; Eggeman et al 2013; Sousa et al 2013).

In spite of extensive research and recent advances in a multimodality management of EBC, recurrences are still common, especially in patients with adverse clinical, pathological and genomic features. Approximately 25%-30% of patients with HR-positive, HER2-negative EBC with multiple (≥4) metastatic regional lymph nodes will recur within 5 years with the therapy that includes AIs (EBCTCG 2015). In addition, worse clinical outcomes are observed in patients with EBC that had residual disease in lymph nodes after neoadjuvant chemotherapy (Mittendorf et al 2011). Therefore, new therapeutic strategies are required to improve clinical outcomes in patients with high risk EBC.

1.1.3 Role of the CDK4/6 pathway in BC

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

Cell cycle progression is regulated by cyclin-dependent serine-threonine protein kinases (CDKs). Extracellular growth and adhesion signals increase the level and function of cyclin D proteins within the cell. In turn, the cyclin D proteins associate with and activate CDK4 and CDK6 (Musgrove et al 2011). CDK4 and CDK6 phosphorylation leads to inactivation of the retinoblastoma protein (Rb) and thus releases E2F, which in turn leads to the transcription initiation of proteins involved in cell cycle propagation and proliferation. The luminal A and B subtypes of BC (85% of which are ER-positive and HER2-negative) have high rates of cyclin D/CDK activation; in the luminal A and B subtypes, cyclin D1 (CCND1) amplifications were observed in 29% and 58%, and CDK4 amplifications were observed in 14% and 25%, respectively (Holm et al 2012; The Cancer Genome Atlas Network 2012). Luminal A subtype tumors also have loss of CDKN2A, which encodes $p16^{INK4A}$, a CDK inhibitor (Beroukhim et al 2010). The luminal subtypes also maintain expression of Rb, which is essential for benefit from treatment with a CDK4/6 inhibitor (Thangavel et al 2011).

Dysregulation of cell cycle checkpoints is common in BC, and in all cancers in general, and may have clinical and therapeutic significance. For example, patients with HR-positive BC exhibiting a gene expression signature of Rb loss had a shorter recurrence-free survival following adjuvant tamoxifen (Bosco et al 2007). A tumor gene expression signature of E2F activation is also associated with higher residual tumor cell proliferation following neoadjuvant AI therapy. Therefore, activation of the CDK4/6-Rb-E2F pathway promotes endocrine resistance, and treatment with a CDK4/6 inhibitor or knockdown of CDK4 expression leads to reactivation of Rb, binding back of E2F and subsequent cell cycle arrest thus abrogating endocrine-resistant cell proliferation.

Selective inhibitors of CDK4/6, such as palbociclib and ribociclib, inhibit proliferation and induce apoptosis in preclinical models of endocrine-resistant breast cancer (Miller et al 2011; Thangavel et al 2011; [Ribociclib Investigator's Brochure]). Both palbociclib and ribociclib demonstrated synergy with endocrine treatments in preclinical studies and efficacy in clinical

studies in patients with HR-positive, HER2-negative advanced BC (Finn et al 2009; [Ribociclib Investigator's Brochure]). Addition of palbociclib to letrozole improved median progression-free survival (PFS) from 10.2 months to 20.2 months (hazard ratio 0.49, 95% CI: 0.32-0.75, p=0.0004) in a randomized, open-label, multicenter phase II study (Finn et al 2015) and from 14.5 months to 24.8 months (hazard ratio 0.58, 95% CI: 0.46-0.72, p<0.0001) in a phase III study in systemic non-adjuvant treatment-naive postmenopausal women with ER-positive, HER2-negative advanced BC (Finn et al 2016). In addition, in a phase III study in 521 pre- and postmenopausal patients with advanced HR-positive, HER2-negative BC that had relapsed or progressed during prior ET, addition of palbociclib to fulvestrant (with ovarian suppression in premenopausal women in both arms) improved median PFS from 3.8 months to 9.2 months (hazard ratio 0.42; 95% CI: 0.32-0.56; p<0.001) (Turner et al 2015). In the subgroup analysis of this study, palbociclib-containing regimen has similar efficacy in pre-/perimenopausal vs post-menopausal women and PFS results were not significantly associated with plasma estrogen (E2) levels (Loibl et al 2016), supporting use of palbociclib in pre-/perimenopausal women.

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

Considering demonstrated efficacy of CDK4/6 inhibitors in the HR-positive, HER2-negative advanced BC, co-targeting the CDK4/6-Rb-E2F pathway with CDK4/6 inhibitors may be a viable strategy to enhance endocrine responsiveness and prevent or delay the development of acquired resistance, and it should be explored in the adjuvant setting too.

1.2 Introduction to investigational treatments and other study treatments

This study includes treatments with ribociclib (LEE011), tamoxifen, anastrozole, letrozole, exemestane, and GnRH agonist (such as goserelin, triptorelin or leuprolide).

1.2.1 Overview of ribociclib

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

1.2.1.1 Non-clinical data

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

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

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

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

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

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

1.2.1.2 Clinical experience

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

1.2.1.2.1 Clinical safety of ribociclib

Clinical safety of ribociclib with endocrine agents such as letrozole, tamoxifen, exemestane and fulvestrant has been being evaluated in several phase I and III combination trials. The recommended dose of ribociclib in combination with these agents was declared as 600 mg once daily on days 1-21 of a 28 day cycle schedule.

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

returning to normal values after treatment discontinuation. Eleven patients (3.3%) presented on treatment QTcF prolongation >480 msec. Serious AEs were reported in 21.3% of patients in the ribociclib arm with 7.5% of serious AEs deemed by investigators as treatment-related. Neutropenia, QT interval prolongation and hepatobiliary toxicity are considered to be important identified risks for ribociclib which appear to be manageable and reversible with adequate monitoring, interruption and/or reduction of ribociclib dosing.

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

1.2.1.2.2 Clinical efficacy with ribociclib

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

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

1.2.1.2.3 Clinical pharmacokinetics of ribociclib

Following oral dosing of the capsule formulation at 600 mg, ribociclib is rapidly absorbed with median T_{max} of 2.40 h (range: 0.683 to 7.82 h). Steady-state plasma C_{max} ranges from 606-6170 ng/mL (geometric mean: 1820 ng/mL or 4.1 µM) and AUC_{0-24h} ranges from 6770-90600 ng*h/mL (geometric mean: 23800 ng*h/mL). The effective $T_{1/2}$ of ribociclib is 32.0 h (range: 8.06 to 97.9 h). Inter-patient variability in C_{max} and AUC is 62% and 66%, respectively, as assessed by geometric coefficient of variation (CV%). LEQ803, an active metabolite of ribociclib, has similar PK characteristics as parent drug. At the 600 mg dose level, LEQ803 accounts for approximately 8% of parent exposure after single and multiple doses. Neither ribociclib nor LEQ803 accumulate substantially following repeated daily administration.

Ribociclib undergoes extensive hepatic metabolism via CYP3A in humans based on in vitro and in vivo studies. Ribociclib is mainly eliminated via hepatic clearance, with renal clearance playing a lesser role in humans. The majority of the administered dose was excreted in feces (69.1%), with a minor amount excreted in urine (22.6%). Ribociclib accounted for approximately 23% of the total radioactivity in plasma ([CLEE011A2102]). The most prominent metabolites in plasma are CCI284 (N-hydroxylation), LEQ803 (N-demethylation), and M1 (secondary glucuronide), each representing <10% of total radioactivity. The clinical activity (pharmacological and safety) of ribociclib is primarily due to parent drug, with a negligible contribution from circulating metabolites.

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

strong CYP3A4 inhibitor (ritonavir) increased ribociclib AUC by 3.2-fold following a single oral dose of 400 mg ribociclib ([CLEE011A2101]). Co-administration of a strong CYP3A4 inducer (rifampicin) decreased ribociclib AUC_{inf} by 89% following a single oral dose of 600 mg ribociclib ([CLEE011A2101]).

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

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

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

1.2.2 Overview of adjuvant endocrine therapy

Tamoxifen and AIs letrozole, anastrozole and exemestane are used for adjuvant use in women with HR-positive early breast cancer. AIs can be used either as an upfront therapy or after 2-3 or 5 years of prior tamoxifen (see Section 1.1.2). The long-term efficacy of both approaches of AIs administration is similar (EBCTCG 2015). Clinical treatment guidelines suggest that there is no compelling evidence showing meaningful clinical efficacy or toxicity differences between the letrozole, anastrozole and exemestane (Gradishar et al 2016), therefore similar precautions and monitoring activities should apply irrespective of type of AI administered. GnRH agonists are used to achieve ovarian suppression in premenopausal women. Tamoxifen (without GnRH agonist) is the adjuvant therapy of choice for men with HR-positive EBC (see Section 1.1.2).

In another Novartis study CLEE011E2301 (MONALEESA-7) an imbalance in the QT prolongation was observed in the subgroup of patients receiving tamoxifen versus non-steroidal aromatase inhibitors in combination with ribociclib while the overall safety profile was comparable. Specifically, a greater than expected QT prolongation was observed in the tamoxifen with placebo group (Tripathy et al 2017). Novartis is continuing to analyze the MONALEESA-7 study results to better understand the efficacy and safety data of combination of tamoxifen and ribociclib. However, due to availability of alternative therapies to tamoxifen in the EarLEE-1 protocol (i.e. letrozole, anastrozole, or exemestane), tamoxifen is not permitted to be used in combination with ribociclib in this study.

1.2.2.1 Overview of letrozole

Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system. Letrozole acts by highly selective inhibition of conversion of androgens (mainly from adrenal glands, the primary source of estrogens in postmenopausal women) to estrogens. Letrozole induces a 75% to 95% decrease of estrogen levels after two weeks of treatment with daily doses of 0.1

to 5 mg, with no significant clinical and laboratory toxicities or changes in levels of other hormones of the endocrine system (Lipton et al 1995; Trunet et al 1996).

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

Letrozole (2.5 mg daily) and ribociclib (600 mg, qd, 3 weeks on/1 week off) did not affect metabolism of each other in a phase Ib/II dose escalation/expansion study ([CLEE011X2107]). Additionally, in a phase III study ([CLEE011A2301]), ribociclib had no effect on letrozole PK based on a comparison of letrozole PK data between treatment groups.

The most frequently reported AEs for letrozole in the adjuvant and extended adjuvant clinical trials were hot flashes, arthralgia/arthritis and myalgia. In general, the observed adverse reactions were mild to moderate in intensity. Adjuvant use of letrozole is associated with a decrease in bone mass density which may lead to osteoporosis and associated bone fractures. Consideration should be given to monitoring bone mass density.

Due to its mechanisms of action, letrozole, as well as other AIs, should not be used for above-mentioned indications in women with an intact ovarian function or in non-castrated men.

Refer to the most recent regional prescribing information for more information on letrozole.

1.2.2.2 Overview of anastrozole

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

Anastrozole is administered orally once daily at a dose of 1 mg, taken with or without food. Anastrozole is metabolized by N-dealkylation, hydroxylation and glucuronidation. Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Renal elimination accounts for approximately 10% of total clearance. The major circulating metabolite of anastrozole lacks pharmacologic activity. Anastrozole metabolism occurs mainly via CYP3A4 and UGT1A4 based on in vitro data (Edevana et al 2013). Therefore, anastrozole metabolism may potentially be affected by co-administration with ribociclib. However, anastrozole has been studied up to doses of 10 mg/day (10-times daily dose) and all doses evaluated were well tolerated with no serious acute toxicities attributed to anastrozole (Plourde et al 1995).

Refer to the most recent regional prescribing information for more information on anastrozole.

1.2.2.3 Overview of exemestane

Exemestane is a steroidal irreversible AI that is initially recognized by the aromatase enzyme as a false substrate and is then transformed through an NADPH-dependent mechanism to an intermediate that binds irreversibly to the enzyme, causing inactivation. Exemestane significantly lowers circulating estrogen concentrations (estradiol, estrone and estrone sulfate), but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone (Goetz et al 2015).

The recommended daily dose of exemestane is 25 mg via oral administration after a meal. Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is metabolized by CYP3A4 and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP1A2, 2C9, 2D6, 2E1 and 3A4 (Buzdar 2003).

Although no formal drug-drug interaction studies have been conducted, significant effects on exemestane clearance by CYP isoenzyme inhibitors appear unlikely. The most frequently reported adverse effects for exemestane are gastrointestinal disturbances, hot flushes, arthralgia, myalgia, sweating, fatigue, and dizziness. Reductions in bone mineral density can occur with long-term use of exemestane. Exemestane is generally well tolerated, and AEs are usually mild to moderate. Androgenic effects were reported in a limited number of patients (Buzdar 2003).

Refer to the most recent regional prescribing information for more information on exemestane.

1.2.2.4 Overview of GnRH agonists

GnRH agonists are synthetic analogues of gonadotropin-releasing hormone that by continuous stimulation of the GnRH receptor achieve desensitization of the pituitary gland to GnRH. GnRH agonists differ from the naturally-occurring GnRH by modification(-s) in the decapeptide structure (usually by amino acid substitution in position 6, but also in positions 9 and 10) to decrease degradation of the molecule. Examples for GnRH agonists for use in this study include but not limited to goserelin, triptorelin or leuprolide. One-month depot formulation of GnRH agonists must be used to suppress ovarian function in premenopausal women in this study as the 3-month depot formulations do not reliably suppress estrogen levels in all patients (Gradishar et al 2016).

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

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

2 Rationale

2.1 Study rationale and purpose

While adjuvant ET for HR-positive EBC is effective in reducing risk of recurrence and improving survival, recurrences are still common, especially in patients with unfavorable clinical, pathological and/or molecular features. These recurrences, mostly in the form of distant metastases, are usually incurable and will eventually translate into BC deaths.

Since addition of CDK4/6 inhibitor ribociclib to ET has proven clinical efficacy with tolerable toxicity profile in HR-positive, HER2-negative advanced BC, its use in the adjuvant setting may decrease risk of recurrences in patients with HR-positive, HER2-negative EBC with high risk for presence of micro-metastatic disease after surgical resection of the primary tumor by

enhancing primary endocrine responsiveness and preventing, or delaying the development of acquired resistance for ET.

Therefore, the purpose of this study was to evaluate the effect of addition of ribociclib to standard adjuvant ET on invasive disease-free survival (iDFS) in patients with HR-positive, HER2-negative EBC with adverse clinical and/or pathological features that predispose patients for an increased risk of recurrence.

The study enrollment was early closed on 12 February 2018. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen). The purpose of this amended protocol is to evaluate the preliminary safety data on the combination of ribociclib + ET in HR+, HER2-negative high-risk EBC patients who enrolled in this study prior to the early closure of the enrollment and to allow patients randomized to ribociclib + ET to continue treatment with ribociclib + ET for a maximum of 26 cycles as long as they stay on study.

2.2 Rationale for the study design

This was a phase III, multicenter, randomized, double-blind, placebo-controlled study to evaluate the addition of ribociclib to standard adjuvant ET in patients with HR-positive, HER2-negative high risk EBC.

The study has been closed to enrollment. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen).

The study included pre- and postmenopausal women with HR-positive, HER2-negative EBC that have high risk of recurrence ("high risk EBC") after standard multimodality therapy.

Pre-menopausal women were included in addition to post-menopausal women since major differences in efficacy and safety of ribociclib are not expected in these populations of patients. In planned subgroup analysis of the palbociclib phase III clinical trial of fulvestrant with ribociclib vs fulvestrant with placebo in patients with advanced HR-positive, HER2-negative BC (ovarian suppression was achieved with goserelin in pre-/perimenopausal patients in both arms), no differences in efficacy and safety profile were observed in pre-/perimenopausal vs postmenopausal patients (Turner et al 2015; Loibl et al 2016). In addition, palbociclib did not alter ovarian function suppression and PFS in pre-/perimenopausal patients was not significantly associated with plasma estrogen (E2) levels (Loibl et al 2016). To mitigate potential differences between pre- and postmenopausal women in this study, randomization by a menopausal status will be employed.

Patients with high risk for recurrence included in this study are the following two groups (the rationale for including each group is provided below):

1. Patients who received adjuvant chemotherapy and have tumor characteristics as defined in the AJCC 8th edition Prognostic Stage Group III (see Table 14-1 in Appendix 1) **Note:** Categorization into AJCC 8th edition Prognostic Stage Group III requires determination of the T- and N-categories, grade of the tumor, and ER and PR status. Axillary lymph node dissection (ALND) is a preferred method for axillary lymph node

staging, however sentinel lymph node (SLN) dissection can be used to determine the N-category as follows:

- no metastasis in SLN - patient is considered having N-category N0,
- at least one tumor metastasis larger than 2.0 mm in 1-2 SLNs in a patient with no clinically-detectable lymph nodes, T1-2 tumors, and no gross extra-nodal tumor extension - patient is considered having N-category N1,
- ALND is required to determine the N-category and Prognostic Stage Group in all other patients.

2. Patients who received neoadjuvant chemotherapy and have 1 or more ipsilateral axillary lymph nodes with residual tumor metastases greater than 2.0 mm in lymph node(-s) and residual tumor greater than 10.0 mm in breast tissue surgical specimen.

The rationale for including patients with the AJCC 8th edition Prognostic Stage Group III in the adjuvant trial of high-risk EBC is based on the fact that Prognostic Stage Groups that incorporate anatomical staging (i.e. T-, N- and M-categories) with histopathological grade and biomarker status (i.e. HR and HER2 status) predict prognosis after standard multimodality treatment (including adjuvant chemotherapy and ET) better than classification based solely on the anatomic extent of the disease (Hortobagyi et al 2017).

Recently, SLN dissection without subsequent ALND in case of metastatic SLN became acceptable practice in selected patients following the results of the ACOSOG Z0011 clinical trial where patients with metastatic SLN were randomized to either ALND or no additional surgery. The trial demonstrated comparable 5-y disease-free survival (83.9% vs 82.2% in SLN dissection only and SLN dissection followed by ALND, respectively) and OS (92.5% vs 91.8%, respectively) between the two arms and less surgical co-morbidity with SLN dissection only (Giuliano et al 2011). This approach has been recommended by several clinical guidelines and consensuses (Coates et al 2015; Senkus et al 2015; Gradishar et al 2016; Lyman et al 2016). Since in the ALND arm of Z0011 ~85% of patients had N1 disease (Giuliano et al 2011), patients who conform with the trial eligibility criteria (T1-2, <3 metastatic SLNs, no clinically-evident nodal disease before the surgery, no gross extranodal tumor extension, no neoadjuvant systemic therapy, and were treated with lumpectomy with adjuvant radiotherapy) can be considered as having N-category N1 for the purpose of assignment these patients to the AJCC 8th edition Prognostic Stage Group.

The rationale for including patients treated with neoadjuvant chemotherapy is that neoadjuvant chemotherapy is one of the recommended treatment options for patients with EBC (see Section 1.1.2). To be eligible for this trial, patients treated by neoadjuvant chemotherapy has to have residual tumors in lymph nodes and breast tissue, since these characteristics were shown to be associated and/or predictive for high risk for recurrence (von Minckwitz et al 2012) and worse DSS (Jeruss et al 2008).

Randomization will be stratified by a menopausal status, stage group and geographical region (see Section 4.1). Menopausal status was selected as a stratification factor since it may reflect different treatment choices and prognosis. Premenopausal women will be combined with men in the same stratum since both men and premenopausal women may have higher recurrence rate compared to postmenopausal women and number of men is expected to be small to make

it as a separate stratum. During the randomization, patients with metastatic SLN(-s) and no ALND will be limited to no more than 20% of the accrual total.

The primary efficacy of the investigational intervention will be evaluated by its effect on the iDFS as it is defined in the STEEP System for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (Hudis et al 2007). The definition of iDFS in the STEEP System is broad, clinically-relevant and includes the most commonly accepted DFS events used in published trials for EBC.

2.3 Rationale for dose and regimen selection

The dose (oral administration of 600 mg daily) and regimen (Days 1-21 of a 28 day cycle) of ribociclib was selected for this study since this dose and regimen were shown to be tolerable and efficacious when combined with ET in clinical trials in patients with HR-positive, HER2-negative advanced BC (see Section 1.1.2). In this trial, ET that is combined with ribociclib or placebo will be administered according to local clinical guidelines and regional prescribing information.

Due to a protracted pattern of recurrences of HR-positive, HER2-negative EBC, with the majority of events observed starting from a year after the surgery (EBCTCG 2015), a short duration (i.e. ≤12 months) of ribociclib treatment might not be sufficient for a meaningful impact on recurrence rate of EBC. In order to provide sufficient ribociclib exposure while balancing potential toxicity of prolonged treatment with the medication, ribociclib (or placebo; both in combination with the ET) will be administered for 26 cycles (approximately 24 months) in this study.

2.4 Rationale for choice of combination drugs

Preclinical and clinical data of co-administration of ET with ribociclib showed that combinations with ET are efficacious in HR-positive, HER2-negative advanced BC, and have reversible and manageable toxicities (see Section 1.2).

Ribociclib will be combined with the standard ET that has been approved for adjuvant treatment of EBC and will include either letrozole, anastrozole, or exemestane, with GnRH agonist (in premenopausal women only) administered according to the local clinical guidelines and regional prescribing information (see Section 1.1.2). In premenopausal women with high risk EBC, ET will include ovarian suppression by GnRH agonist. GnRH agonist will be administered every 4 weeks subcutaneously.

2.5 Rationale for choice of comparators drugs

Since, all patients randomized to placebo discontinued study participation at the end of safety follow up, this section is longer applicable.

2.6 Risks and benefits

Based on preclinical and clinical data, treatment of ribociclib in combination with ET is expected to be tolerable and toxicities of the treatment are expected to be manageable and reversible upon dose reduction, treatment interruption or discontinuation.

Patients in this study will be carefully monitored for key toxicities that have been observed with ribociclib (see Section 1.2.1) or endocrine treatments (see Section 1.2.2). Risk will be further minimized by adherence to inclusion/exclusion selection criteria (see Section 5), avoidance of prohibited medication (see Section 6.3.3), close safety monitoring (see Section 8) and dose adjustment guidelines (see Section 6.2).

Since the study was closed to enrollment and all patients were unblinded, the Novartis study team will monitor safety in conjunction with the Novartis Safety Management Team.

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
To evaluate the preliminary safety and tolerability of the ribociclib + ET in patients that were randomized to ribociclib + ET prior to the early closure of enrollment.	Tolerability and Safety of the treatment regimen based on frequency and severity of AEs, laboratory and ECG abnormalities	
The study has an early enrollment closure. All randomized patients were unblinded. Health related quality of life, hospital resource utilization, blood and tissue samples for biomarkers will no longer be collected and analyzed.		

4 Study design

4.1 Description of study design

This was a randomized, phase III, double-blind, placebo-controlled, multi-center, international study to evaluate efficacy and safety of ribociclib with ET as an adjuvant treatment in patients with HR-positive, HER2-negative, high risk EBC.

The study has been closed to enrollment. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen). Patients randomized to placebo have to complete 30-day safety follow up after the last dose of placebo.

Following the protocol amendment 02, this study is an open label, multi-center phase II conducted in the US only.

The study will include

- Screening phase (28 days); this phase has been completed for all patients as of 12 February 2018
- Treatment phase composed of 26 cycles of ribociclib treatment (approximately 24 months) in combination with ET (where treatment with ET may start up to 12 weeks before the date of randomization) and 30 days safety follow up from last dose of ribociclib;

During treatment phase, patients will be treated with combination of ribociclib + ET for a maximum of 26 cycles or until disease recurrence, intolerable toxicity, withdrawal of consent, or discontinuation from the study treatment for any other reason, whichever is earlier.

Starting with the protocol amendment 02, post-treatment follow-up phase assessments are not performed. For each patient randomized to placebo + ET, study participation will end following the safety follow-up after the end of treatment (EOT) within 30 days from the last dose of placebo. For each patient randomized to ribociclib + ET, study participation will end following the safety follow-up after the EOT after the last dose of ribociclib. Patients in follow-up phase will end study participation following the protocol amendment 02.

4.1.1 Screening phase

Pre- or post-menopausal women with high risk HR-positive, HER2-negative EBC who provided written informed consent will be screened for eligibility during the period up to 28 days immediately prior to starting ribociclib or placebo in combination with the standard adjuvant endocrine therapy (ET) prescribed by the investigator (tamoxifen, letrozole, anastrozole, or exemestane, with GnRH agonist for premenopausal women; only tamoxifen will be allowed to be used in men). ET may start ≤ 12 weeks prior to randomization.

During the screening phase the investigator must:

- Obtain signed informed consent from the patient prior to any study procedures
- Assess the inclusion and exclusion criteria as detailed in Section 5
- Perform all screening procedures as detailed in Table 7-1

Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to enrollment of each patient into the study to assure that all inclusion and exclusion criteria have been satisfied.

4.1.2 Treatment phase

Ribociclib will be given orally once a day on days 1 to 21 in each 28 day cycle. Standard adjuvant ET will be administered according to the local clinical guidelines and regional prescribing information. Acceptable ET in women includes letrozole 2.5 mg by mouth daily, or anastrozole 1 mg by mouth daily, or exemestane 25 mg by mouth daily. In premenopausal women, ET, besides AI, should include a GnRH agonist administered every 4 weeks (examples include but not limited to goserelin, triptorelin or leuprolide). Patients receiving GnRH agonist should be regularly monitored per local institutional clinical guidelines to confirm a postmenopausal value of gonadotropin and sex hormones according to local laboratory ranges.

Study treatment will continue until completion of a maximum of 26 cycles of ribociclib treatment (approximately 24 months), first recurrence (any of the following or combination of local, regional or distant recurrences, or contralateral invasive breast cancer, or second primary non-breast invasive cancer), intolerable toxicity, withdrawal of consent by the patient, patient is lost to follow up, death, or discontinuation from the study treatment due to any other reason or the sponsor terminates the study, whichever is earlier.

During treatment with ribociclib, investigators will not be allowed to change ET unless intolerable toxicity, patient's request, or any other medically-important event that requires change of ET (Investigator should clearly document in the eCRF the reason for changing of ET during the treatment with ribociclib. After end of treatment with ribociclib no further information will be collected after the safety follow-up assessment 30 days after the last dose of ribociclib. Patients who permanently discontinue adjuvant ET for any reason and do not re-initiate any adjuvant ET, must discontinue ribociclib and complete the safety follow-up 30 days from the last dose of ribociclib. Patients who permanently discontinue ribociclib, will undergo the safety follow-up assessment for 30 days after the last dose of ribociclib assessments.

Recurrence will be assessed by the investigator periodically as clinically indicated, or at any time when recurrence is suspected. The end of the study for a given patient is defined when the patient permanently discontinues ribociclib and all the end of trial procedures for that individual patient are completed at the end of the safety follow-up assessment.

Safety will be assessed for each patient until 30 days after the last dose of ribociclib and will include routine safety monitoring except in case of death, loss to follow up or withdrawal of consent.

4.1.3 Follow up phase

4.1.3.1 Post treatment follow-up

Starting with the protocol amendment 02, follow-up phase assessments are not performed.

4.1.3.2 Survival follow up

Starting with the protocol amendment 02, survival follow up will not be performed.

The end of the study for a given patient is defined when the patient permanently discontinues study specified treatments and all the end of trial procedures for that individual patient are completed. For a patient randomized to placebo + ET, study participation will end following the safety follow-up after the end of treatment (EOT) after the last dose of placebo. For patient randomized to ribociclib + ET, study participation will end following the safety follow-up within 30 days from the last dose of ribociclib.

4.1.3.3 Timing of interim analyses and design adaptations

Following early enrolment closure and unblinding of the patients' randomization arm, the interim analyses are no longer planned. The final data analysis is planned to be performed after all patients discontinue the ribociclib treatment and complete the safety follow-up assessment 30 days after the last patient's last dose of ribociclib.

4.2 Definition of end of study

The end of study will be declared after all patients have discontinued ribociclib treatment and completed the safety follow-up period (until 30 days after last dose of ribociclib. The end of study may be declared also when the last patient on treatment has been enrolled in another

Novartis-sponsored protocol that will allow treatment continuation for patients who benefited from the study treatment with ribociclib.

The study is expected to continue for maximum approximately 25 months (24 months + 30 day follow-up) and will end once the last patient randomized to ribociclib has completed safety their follow-up safety assessment within 30 days after the last dose of ribociclib.

4.3 Early study termination

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

5 Population

5.1 Patient population

The study includes men and pre- and postmenopausal women with HR-positive, HER2-negative high risk EBC after adequate surgical resection, radiotherapy (if indicated), adjuvant or neo-adjuvant chemotherapy, and who are deemed to be eligible for adjuvant ET for at least 60 months of duration.

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

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 study has been closed to enrollment. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen).

5.2 Inclusion criteria

The protocol includes patients that were eligible under following eligibility criteria.

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

1. Written informed consent must be obtained prior to any screening procedures
2. Patient is a female with known menopausal status at the time of initiation of (neo-) adjuvant therapy/GnRH agonist or male adult ≥18 years-old at the time of informed consent
   Note: Postmenopausal status is defined when:
   - patient underwent bilateral oophorectomy, or
   - age ≥ 60 years, or

- age < 60 years and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, or ovarian suppression) and FSH and plasma estradiol are in the postmenopausal ranges per local normal range, or
- For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol per local clinical guidelines are required for determination of postmenopausal status

All non postmenopausal women are considered premenopausal

3. Patient with histologically confirmed unilateral primary invasive adenocarcinoma of the breast
4. Patient has breast cancer that is positive for estrogen-receptor and/or progesterone-receptor (determined on the most recently analyzed tissue sample and tested by a local laboratory based on the ASCO-CAP Guidelines (Hammond et al 2010))
5. Patient has HER2-negative breast cancer defined as a negative *in situ* hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative *in situ* hybridization (FISH, CISH, or SISH) test is required (based on the most recently analyzed tissue sample and all tested by a local laboratory)
6. Patient has available archival tumor tissue from the surgical specimen
7. Patient after surgical resection where tumor was removed completely, with the final surgical specimen microscopic margins free from tumor, and:
   - Patients who received adjuvant chemotherapy and have tumor characteristics as defined in the AJCC 8th edition Prognostic Stage Group III (see Table 14-2 in Appendix 1)
     Note: Categorization into AJCC 8th edition Prognostic Stage Group III requires determination of the T- and N-categories, histopathological grade of the tumor and ER and PR status. ALND is a preferred method for axillary lymph node staging, however SLN dissection can be used to determine the N-category as follows:
     - no metastasis in SLN - patient is considered as having N-category N0,
     - at least one tumor metastasis larger than 2.0 mm in 1-2 SLNs in a patient with no clinically-detectable lymph nodes, T1-2 tumors, and no gross extra-nodal tumor extension - patient is considered as having N-category N1. (This category of patients with metastatic SLN and no ALND will be limited to no more than 20% of the total accrual),
     - ALND is required to determine the N-category and Prognostic Stage Group in all other patients,

   or

   - Patients who received neoadjuvant chemotherapy and have 1 or more ipsilateral axillary lymph nodes with residual tumor metastases greater than 2.0 mm in lymph node(-s) and residual tumor greater than 10.0 mm in breast tissue surgical specimen
8. Patient has completed multi-agent adjuvant or neoadjuvant chemotherapy of ≥ 4 cycles or ≥ 12 weeks in duration which included taxanes in the regimen
9. Patient has completed adjuvant radiotherapy (if indicated) according to the institutional guidelines prior to screening

10. Patient has no contraindication for the adjuvant ET and is planned to be treated by ET for 5 years or more
11. Patient may already have initiated ET at the time of randomization, but randomization must take place within 52 weeks of date of initial histological diagnosis of breast cancer and within 12 weeks of initiating standard adjuvant ET. Ovarian suppression for fertility preservation is not considered adjuvant ET
12. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
13. 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
    - Estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min by a Cockcroft-Gault formula.
    - Alanine transaminase (ALT) $\leq 1.5 \times$ ULN
    - Aspartate transaminase (AST) $\leq 1.5 \times$ ULN
    - Total serum bilirubin $\leq$ ULN; or total bilirubin $\leq 3.0 \times$ ULN with direct bilirubin $\leq 1.5 \times$ ULN of the central laboratory in patients with well documented Gilbert's Syndrome
    - International normalized ratio (INR) $\leq$ 1.5 (unless the patient is receiving anticoagulants and the INR is within the therapeutic range of intended use for that anticoagulant within 7 days prior to the first dose of study drug)
    - Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements (the central laboratory value should be documented within normal limits after the correction) before the first dose of study drug:
        - Sodium
        - Potassium
        - Phosphorus
        - Magnesium
        - Total Calcium
14. Standard 12-lead ECG values defined as the mean of the triplicate ECGs and assessed by the central laboratory:
    - QTcF interval (using Fridericia's correction) at screening < 450 msec
    - Mean resting heart rate 50-90 bpm (determined from the ECG)
15. Subjects must be able to communicate with the investigator and comply with the requirements of the study procedures
16. Must be willing to remain at the clinical site as required by the protocol

17. Premenopausal women must have confirmed negative pregnancy test (for β-hCG) during the screening period and before starting study treatment unless this patient had a hysterectomy
18. All sexually active male patients are required to 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 ribociclib via seminal fluid.

5.3 Exclusion criteria

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

1. Patient has received any CDK4/6 inhibitor
2. Patient has received prior treatment with tamoxifen, raloxifene or AIs for reduction in risk ("chemoprevention") of breast cancer and/or treatment for osteoporosis within last 2 years prior to screening
3. Patient has received prior treatment with anthracyclines at cumulative doses of 450 mg/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, ET and placebo (e.g. rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption, and soy allergy)
5. Patient with distant metastases of breast cancer beyond regional lymph nodes
6. Patient is concurrently using other anti-neoplastic therapy with the exception of adjuvant ET (for duration of no more than 12 weeks) from the date of randomization
7. Patient has had major surgery, chemotherapy or radiotherapy within 14 days prior to starting treatment with ribociclib or placebo
8. Patient has not recovered from clinical and laboratory acute toxicities of chemotherapy, radiotherapy and surgery (i.e., patient has AEs attributed to prior anti-neoplastic therapy NCI CTCAE version 4.03 grade ≥1 at day of enrollment, excluding alopecia and amenorrhea)
9. Patient has a concurrent malignancy or malignancy within 5 years prior to screening, with the exception of adequately treated, basal or squamous cell carcinoma of the skin or curatively resected cervical carcinoma *in situ*
10. Patient has a history of HIV infection (testing is not mandatory)
11. Patient has active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (testing is not mandatory)
12. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, including any of the following:
    - History of documented myocardial infarction (MI), angina pectoris, symptomatic pericarditis, or coronary artery bypass graft (CABG) within 6 months prior to study entry
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) (testing not mandatory)

- Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
  - Risk factors for Torsades de Pointe (TdP) including uncorrected 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 TdP that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug)
  - Inability to determine the QTcF interval
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
- Uncontrolled hypertension with systolic blood pressure (SBP) >160 mmHg

13. Patient is currently receiving any of the following substances and these cannot be discontinued 7 days before the first dose of study drug:
    - Concomitant medications, herbal supplements, and/or fruits (e.g., grapefruit, pumeloes, star fruit, Seville oranges) and their juices that are known as strong inhibitors or inducers of CYP3A4/5
    - Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
14. 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)
15. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., uncontrolled ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
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, liver cirrhosis or any other significant liver disease, active untreated or uncontrolled fungal, bacterial or viral infections, active infection requiring systemic anti-bacterial therapy, etc.) or limit life expectancy to ≤5 years
17. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer
18. Pregnant or breast-feeding (lactating) women or women who plan to become pregnant or breast-feed during the study.
19. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception

during the study treatment and for 21 days after stopping the study treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization (at least 6 months prior to screening). For female patient on the study the vasectomized male partner should be the sole partner for that patient.
- Placement of an intrauterine device (IUD)

Note: Use of oral (estrogen and progesterone), transdermal, injected or implanted hormonal methods of contraception as well as hormonal replacement therapy is not allowed in this study

Note: Women are considered not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment she is considered not of child bearing potential

Note: After the end of study treatment and while on standard endocrine treatment, women of child-bearing potential and men should use effective contraception according to the local prescribing information

6 Treatment

6.1 Study treatment

For this study, the term “investigational or study drug” refers to Novartis study drug ribociclib. The other drugs to be used in this study are endocrine therapy (ET), which will be administered according to the local clinical guidelines and regional prescribing information depending on patient’s needs and according to the investigator’s clinical judgement.

“Study treatment” in this study refers to the combination of the ET with ribociclib. ET alone after discontinuation of the ribociclib is not considered a “study treatment”.

Ribociclib will be supplied by Novartis or its designee in the form of 200 mg tablets as individual patient supply packaged bottles. ET will be sourced locally according to local practices and regulations in each participating country. 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 ribociclib and ET dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded in the eCRF.

6.1.1 Dosing regimen

All eligible patients will receive starting from Cycle 1 Day 1

- Ribociclib 600 mg tablets once daily on days 1 to 21 of a 28 day cycle + ET

Ribociclib will be given orally once a day on days 1 to 21 in each 28 day cycle. Days 22 to 28 will be a "rest" from ribociclib (Table 6-1). Treatment of ribociclib + ET will continue for 26 cycles (approximately 24 months).

ET will be administered according to the local clinical guidelines and regional prescribing information (Table 6-1). Acceptable ET that will be combined with ribociclib in female patients includes one of the following medications:

- Letrozole 2.5 mg by mouth daily,
- Anastrozole 1 mg by mouth daily,
- Exemestane 25 mg by mouth daily.

In pre-menopausal women, ET will include also a GnRH agonist (examples include, but not limited to, goserelin, triptorelin or leuprolide) administered every 4 weeks. Patients receiving GnRH agonist will be monitored regularly per local institutional clinical guidelines to confirm a post-menopausal value of gonadotropin and sex hormones according to local laboratory ranges (see Table 7-3).

Patients will be allowed to start ET up to 12 weeks before the day of randomization. During treatment with ribociclib, investigators will not be allowed to change ET unless intolerable toxicity, patient's request, or any other medically important event that requires change of ET (Investigator must clearly document in the eCRF the reason for changing of ET during the treatment with ribociclib).

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Ribociclib	Tablets for oral use	600 mg	Once daily on days 1 to 21 in each 28 day cycle
Letrozole	Tablets for oral use	2.5 mg	Days 1 to 28 of a 28 day cycle
Anastrozole	Tablets for oral use	1 mg	Days 1 to 28 of a 28 day cycle
Exemestane	Tablets for oral use	25 mg	Days 1 to 28 of a 28 day cycle
GnRH agonists	Per local prescribing information		Day 1 of a 28 day cycle

Ribociclib will be administered as a flat-fixed dose, and not by body weight or body surface area. There will 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 study has been closed to enrollment. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen). Patients randomized to placebo permanently discontinued treatment and completed the safety follow-up assessment. Patients randomized to ribociclib are allowed to continue treatment with ribociclib + ET for a maximum of 26 cycles (approximately 24

months) or until first disease recurrence, intolerable toxicity, withdrawal of consent, death or discontinuation from the study treatment for any other reason, whichever is earlier.

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

6.1.1.1 General dosing guidelines

Study treatments should be taken as follows:

- Ribociclib is dosed for the first 21 days of the 28-day cycle.
- 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 may take ribociclib at home.
- Patients should be instructed to take ribociclib and ET with a large glass of water (~250 mL or ~8 oz) at the same time each day. Patients can determine if they prefer morning or early afternoon dosing, but they should maintain a consistent time. Evening doses are strongly not recommended.
- Ribociclib can be administered with or without food.
- Patients should be instructed to swallow the tablets whole and not to chew, crush or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF. Refer to Section 6.3.1.4 for use of anti-emetic medications.
- 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, pomegranates or products containing the juice of each during the entire study treatment and preferably 7 days before the first dose of study drug. These foods are known as CYP3A4 inhibitors and have a potential to increase exposure to ribociclib.

  Note: Oranges and orange juice are allowed. Herbal or dietary supplements known as strong inhibitors or inducers of CYP3A4 are prohibited.
- Multivitamins, glucosamine, probiotics, fish oil are permitted.
- GnRH agonist must be administered by injection every 28 days in accordance with the regional prescribing information.

6.1.1.2 Additional dosing guidelines for ECG panel collection

On days with ECG panel, the following additional guidelines should be followed:

- If a pre-dose ECG measurement is to be collected, then the ECG measurement should occur before dosing the study treatment.

6.1.2 Guidelines for continuation of treatment

For guidelines for continuation of treatment with ribociclib, see Section 6.2 "Dosing modification".

Patients who permanently discontinue ribociclib for any reason are considered to have completed the treatment phase and will proceed to End of Treatment (EOT) visit.

After End of Treatment, patents may continue on the same ET regimen or another ET regimen as determined by the Investigator according to local clinical guidelines and regional prescribing information depending on patient's needs and according to the investigator's clinical judgement. Patients who permanently discontinue ET during the treatment phase will also discontinue ribociclib and will move to End of Treatment.

6.1.3 Study treatment duration

The study has been closed to enrollment. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen).

Patients will be treated with ribociclib + ET for 26 cycles (approximately 24 months) until first recurrence, intolerable 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, whichever is earlier.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow patients to continue the study treatment (Table 6-2). These dose changes must be recorded on the Dosage Administration Record CRF.

Table 6-2 Dose modification guidelines

	Ribociclib	
	Dose	**Number of tablets & strength**
Starting dose	600 mg	3 x 200 mg tablets
First dose reduction	400 mg	2 x 200 mg tablets
Second dose reduction	200 mg	1 x 200 mg tablet

6.2.1.1 Ribociclib

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

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

ribociclib must be discontinued. If dosing was interrupted for >28 days due to ribociclib-related toxicity, ribociclib must be discontinued and study participation will end with the safety assessment 30 days after the last dose of ribociclib.

Unscheduled local laboratory assessments may be performed and recorded in the eCRF if required according to the visit evaluation schedule, for documentation of adverse event, for treatment decision and any clinically significant laboratory values per investigator's discretion.

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used, with exception of FSH and plasma estradiol levels to determine menopausal status.

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

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

Toxicity/Grade	Dose Adjustment and Management Recommendations
Anemia (Hemoglobin)	
Grade 1 (≥10.0 – LLN g/dL)	No dose adjustment required.
Grade 2 (≥8.0 – <10.0 g/dL)	No dose adjustment required.
Grade 3 (<8.0 g/dL)	Dose interruption until recovery to grade ≤ 2. Re-initiate ribociclib at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

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

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48-72h later)	Maintain dose level with LFTs monitored bi-weekly
Grade 2 (> 1.5 – 3.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level If resolved to ≤ grade 1 in > 21-28 days or toxicity recurs, then reduce 1 dose level Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions, or recovery to ≤ grade 1 is > 28 days, discontinue ribociclib
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of ribociclib, until resolved to ≤ grade 1, then lower 1 dose level of ribociclib Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If resolved to ≤ grade 1 in > 28 days or toxicity recurs, discontinue ribociclib
Grade 4 (> 10.0 x ULN)	Discontinue ribociclib
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of liver metastases, evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile ducts 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
Grade 2 (> 3.0 – 5.0 x ULN)	Dose interruption of ribociclib If resolved to ≤ baseline grade in ≤ 21 days, then maintain dose level If resolved to ≤ baseline grade in > 21 days or toxicity recurs, then reduce 1 dose level Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
Grade 3 (> 5.0 – 20.0 x ULN)	Dose interruption of ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If recovery to ≤ baseline grade is > 28 days, discontinue ribociclib If toxicity recurs, discontinue ribociclib
Grade 4 (> 20.0 x ULN)	Discontinue ribociclib
AST or ALT and concurrent Bilirubin	
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT >3.0 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis **Or** For patient with elevated AST or ALT or total bilirubin at baseline: baseline: [AST or ALT >2 x baseline AND >3.0x ULN] OR [AST or ALT >8.0 x ULN]- whichever is lower- **combined with** [total bilirubin > 2 x baseline AND >2.0 x ULN]	Discontinue ribociclib
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, liver metastases, and alcohol intake.	

Refer to Section 6.2.2.1 for additional follow-up on potential drug-induced liver injury (DILI) cases.

6.2.1.2 Dose adjustments for QTcF prolongation

To determine QTcF duration to use in the following table, measurements of QT interval should be conducted on ECG and corrected (QTcF).

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

Grade	Dose Modification
For All Grades	1. Check the quality of the ECG and the QT value and repeat if needed. 2. Perform analysis of serum electrolytes (sodium, potassium, calcium, phosphorus, magnesium). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. 3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib.
1 QTcF 450-480 msec	Perform steps 1-4 as directed in “For All Grades.” No dose adjustment required.
2 QTcF 481-500 msec	Interrupt ribociclib. Perform steps 1-4 as directed in “For All Grades.” Perform a repeat ECG within one hour of the first QTcF of ≥ 481 msec. Repeat ECG as clinically indicated until the QTcF returns to < 481 msec. Restart ribociclib with dose reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. If QTcF ≥ 481 msec recurs, ribociclib should be reduced again by 1 dose level. Refer to Table 6-2 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 ≥ 481 msec

3 QTcF ≥ 501 msec on at least two separate ECGs	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Perform a repeat ECG within one hour of the first QTcF of ≥ 501 msec. ● If QTcF remains ≥ 501 msec, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to < 481 msec. ● If QTcF returns to < 481 msec, ribociclib will be reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. ● If QTcF remains ≥ 481 msec after performing steps 1-4 as directed in "For All Grades, discontinue ribociclib. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 msec If QTcF of ≥ 501 msec recurs, discontinue ribociclib
4 [QT/QTcF ≥ 501 or > 60 msec change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	Discontinue ribociclib. Perform steps 1-4 as directed in "For All Grades." Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 msec

6.2.1.3 Guidance for all other adverse reactions

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

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

For all other AEs please follow recommendations in Table 6-6.

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

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

6.2.2 Follow-up for toxicities

Patients who complete treatment or whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed at least weekly for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event.

All patients will be followed for safety (routine safety monitoring) for approximately 30 days following the last dose of ribociclib. Once an AE is detected, investigators are required to follow this AE until its resolution or stabilization. Refer to Section 8.1.1 for definitions and reporting of AEs. After 30 days, SAEs that are deemed by the investigator to be related to the study treatment (i.e., combination of ribociclib and ET) or ET alone will continue to be reported, until withdrawal of consent, death, loss to follow up, or the end of study, whichever is earlier.

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

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

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 (i.e. ≤ ULN) 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 (i.e. > ULN) 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**. 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 liver metastases
- 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.
- Considering liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury

All cases of DILI confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant", thus met the definition of SAE (Section 8.2.1), and must be reported as SAE using the term "potential drug-induced liver injury". All events must be followed up with the outcome clearly documented. Results of tests as well as other clinically important information will be recorded in the eCRF.

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed. Potential drug interaction between ribociclib and concomitant medications should always be taken into consideration.

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 treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications / Relevant Non-Drug Therapies CRF.

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

6.3.1.1 Use of bisphosphonates and denosumab

Bisphosphonates and denosumab are generally allowed per local/regional prescribing information and clinical guidelines. Administration and reason for bisphosphonate/denosumab use must be clearly documented in the eCRF. Refer to regional prescribing information and

clinical guidelines for comprehensive safety and efficacy information and guidance for each medication.

6.3.1.2 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing ribociclib drug exposure to sub-therapeutic 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).

6.3.1.3 Hematopoietic growth factors

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

6.3.1.4 Use of antiemetic medications

Ribociclib has minimal to low emetogenic potential according to a definition of anti-neoplastic agent emetogenicity (Grunberg et al 2010). Antiemetic therapy can be used according to clinical guidelines for anti-neoplastic medications with low to minimal emetogenic potential for treatment and/or prevention of nausea and vomiting as a result of study treatment (NCCN 2016; Roila et al 2016).

Potential drug interaction between ribociclib and antiemetic medications should always be taken into consideration. Example of prohibited antiemetic medication is intravenously administered ondansetron that in combination with ribociclib may precipitate TdP. Refer to Section 6.3.2 and Section 6.3.3 for list of medications that are allowed or prohibited to be used with ribociclib.

6.3.2 Permitted concomitant therapy requiring caution

Medications to be used with caution during combined ribociclib and ET in this study (see Table 14-4 in Appendix 2) are listed below. These medications should be avoided if possible. If they must be given based on the investigator's judgment, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time.

Following medications should be used with caution and with proper clinical and laboratory monitoring:

- Medications that carry a possible risk for QT prolongation and/or Torsades de Pointes (TdP) (may precipitate QT prolongation and TdP; see Section 6.3.3.2 for additional details).
- Moderate inhibitors or inducers of CYP3A4/5 (may increase or decrease ribociclib exposure, respectively - see Section 1.2.1.2.3 for additional details).
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index (ribociclib may increase exposure to these medications - see Section 1.2.1.2.3 for additional details).

- Based on *in vitro* data (see Section 1.2.1.1 for additional details), co-administration of ribociclib with strong inhibitors of BSEP (see Table 14-4 in Appendix 2) may lead to intrahepatic cholestasis, and co-administration of ribociclib with sensitive substrates of MATE1, OCT2, and BCRP has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements.

6.3.3 Prohibited concomitant therapy

The following medications are prohibited during combined ribociclib and ET treatment in this study (Table 14-4 in Appendix 2):

- Strong inhibitors or inducers of CYP3A4/5 (may significantly increase or decrease ribociclib exposure, respectively)
- Herbal medications/preparations that are strong inhibitors or inducers of CYP3A4/5. These include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, DHEA, yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications at least 7 days prior to first dose of study treatment.
- Substrates of CYP3A4/5 with a narrow therapeutic index (ribociclib may increase exposure to these medications resulting in toxicity to these medications)
- Medications with a known risk for QT prolongation and/or TdP (may precipitate QT prolongation and TdP in combination with ribociclib)
- Hormonal contraception, or hormonal medications used as a hormonal replacement therapy for symptoms of menopause (as these have potential to reduce efficacy of ET)
- Other investigational and anti-neoplastic therapies

6.3.3.1 Concomitant medications associated with menopausal status

It is important to consider potential drug-drug interactions when using concomitant medications associated with hot flushes and other anticipated symptoms associated with this indication/use of ET. Use of systemically administered medications containing estrogens is not allowed (see Section 6.3.3). Please see Table 14-3 in Appendix 2 for further information on prohibited concomitant medications.

6.3.3.2 Drugs with QT prolongation

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

6.3.4 Other procedures

Use of AIs may cause decrease in bone mineral density. Consider bone mineral density monitoring in patients receiving AIs, and appropriate preventive or therapeutic measures for osteopenia and osteoporosis in these patients per local clinical guidelines.

Use of letrozole or anastrozole may cause increase in total blood cholesterol. Consider monitoring cholesterol, and taking appropriate preventive or therapeutic measures in patients receiving AIs per local clinical guidelines.

Please refer to regional prescribing information of specific endocrine agent for additional procedures and supportive measures required during administration of ET.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

The study has been closed to enrollment. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen).

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 remote data capture (RDC) interface.

The investigator or designated staff will contact the interactive response technology (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.

6.4.2 Treatment assignment or randomization

Since the study has been closed to enrollment and no new patients will be randomized, this section is no longer applicable.

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

Randomization will be stratified by

- Menopausal status: (premenopausal women/men) vs (postmenopausal women),
- Stage group (AJCC 8th edition Prognostic Stage Group IIIA) vs (AJCC 8th edition Prognostic Stage Groups IIIB/C) vs (residual disease after neoadjuvant chemotherapy),

- Geographical region: (North America/Europe/Australia) vs (rest of the world).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication 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 contact 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 ribociclib/placebo to be dispensed to the patient in combination with ET at Cycle 1 Day 1 no later 3 days after the randomization of the patient. The randomization number will not be communicated to the caller.

6.4.3 Treatment blinding

Since all randomized patients were unblinded, this section is no longer applicable.

6.5 Study drug preparation and dispensation

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

Letrozole, anastrozole, exemestane and GnRH agonist should be dispensed and administered according to local prescribing information and practice.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Ribociclib and other study treatments 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 in the eCRF.

6.5.1 Study treatment packaging and labeling

Ribociclib/placebo will be provided as global clinical blinded supply and will be packed and labeled under the responsibility of Novartis Drug Supply Management (see Table 6-7 and Table 6-8).

Following the protocol amendment 02, only ribociclib will be dispensed to patients.

Ribociclib/placebo 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. Responsible site

personnel will identify the 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 6-7 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Ribociclib/placebo	Tablets in bottles	Study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment arms.
Anastrozole	Refer to local product information	Refer to local product information
Letrozole	Refer to local product information	Refer to local product information
Exemestane	Refer to local product information	Refer to local product information
GnRH agonist	Refer to local product information	Refer to local product information

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Ribociclib Investigator's Brochure].

Table 6-8 Supply and storage of study treatments

Study treatments	Supply	Storage
Ribociclib	Centrally supplied by Novartis	Refer to study treatment label
Anastrozole	Locally according to local practices and regulations in each participating country	Refer to local product information
Letrozole	Locally according to local practices and regulations in each participating country	Refer to local product information
Exemestane	Locally according to local practices and regulations in each participating country	Refer to local product information
GnRH agonist	Locally according to local practices and regulations in each participating country	Refer to local product information

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug

Accountability Form. This information must be captured in the source document at each patient visit.

6.5.3.2 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.

6.5.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column). No CRF will be used as a source document.

Allowed visit windows are specified as follows:

- Screening assessments, apart from those listed below, must occur within 28 days prior to the randomization as per Table 7-1.
- 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 a general ±3 days visit window is permitted on assessments to take into account scheduling over public holidays, if not explicitly specified otherwise.
- Radiological and histological assessments must be performed as outlined in Table 7-1. A visit window of ± 2 weeks is allowed unless otherwise specified.
- Every effort should be made to follow the schedule outlined in Table 7-1.
  At the time of the protocol amendment 02, all patients have been randomized.

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening phase	Treatment phase Ribociclib + endocrine therapy (26 cycles / approx. 24 months)							
Visit Name			**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3 to 6**	**Cycles 7 to 26 (every 3 cycles from C7D1)**	**End of treatment**	**Safety follow up**
Study/treatment cycle day			**-28 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose of ribociclib**	**Last dose of ribociclib + 30 days**
Screening											
Obtain Study Informed Consent	D	7.1.1	X								
IRT Screening (after ICF)	D	7.1.1	X								
Disposition assessment											
End of phase disposition	D	7	X							X	
Patient history											
Demography	D	7.1.1.3	X								
Inclusion/exclusion criteria	D	7.1.1.3	X								
Medical history	D	7.1.1.3	X								
Diagnosis, stage and grade of cancer	D	7.1.1.3	X								
ER status	D	7.1.1.3	X								
PgR status	D	7.1.1.3	X								
HER2 status	D	7.1.1.3	X								
Prior anti-neoplastic therapies	D	7.1.1.3	X								
Prior/concomitant	D	7.1.1.3	Continuous, up to 30 days after last dose of ribociclib								

	Category	Protocol Section	Screening phase	Treatment phase Ribociclib + endocrine therapy (26 cycles / approx. 24 months)							
Visit Name			**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3 to 6**	**Cycles 7 to 26 (every 3 cycles from C7D1)**	**End of treatment**	**Safety follow up**
Study/treatment cycle day			**-28 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose of ribociclib**	**Last dose of ribociclib + 30 days**
medications											
IRT Dispensation											
IRT ribociclib dispensation	S	7.1.1.1		X		X		X	X (every cycle)		
Physical examination											
Physical examination	S	7.2.2.1	X			X		X	X	X	
Vital signs	D	7.2.2.2	X	X	X	X		X	X	X	
Weight	D	7.2.2.3	X	X	X	X		X	X	X	
Height	D	7.2.2.3	X								
Menopausal status assessment											
Menopausal status	D	7.2.2.5.5	X	Every 12 months or as clinically indicated							
Laboratory assessments											
Hematology	D	7.2.2.5.1	X		X	X	X	X	X	X	
Biochemistry	D	7.2.2.5.2	X		X	X	X	X	X	X	
Coagulation	D	7.2.2.5.3	X	As clinically indicated							
Urinalysis	D	7.2.2.5.4	X	As clinically indicated							
Serum pregnancy test (for women of child bearing potential only)	D	7.2.2.5.5	X							X	
Urine pregnancy test (for women of child bearing potential only)	D	7.2.2.5.5		X		X		X	X (every cycle)		

	Category	Protocol Section	Screening phase	Treatment phase Ribociclib + endocrine therapy (26 cycles / approx. 24 months)							
Visit Name			**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3 to 6**	**Cycles 7 to 26 (every 3 cycles from C7D1)**	**End of treatment**	**Safety follow up**
Study/treatment cycle day			**-28 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose of ribociclib**	**Last dose of ribociclib + 30 days**
Recurrence assessment											
Clinical evaluation for recurrence	D		X	After randomization as clinically indicated, or at any time when recurrence is suspected							
Mammography (unless bilateral mastectomy)	D	7.2.1	X (unless done within previous 12 months)	As clinically indicated, or at any time when recurrence is suspected							
Radiological evaluation (CT, MRI, US, PET, bone scan, X-ray or mammography)	D	7.2.1	If clinically indicated	As clinically indicated, or at any time when recurrence is suspected							
Histological (or cytological, when applicable)	D	7.2.1	If clinically indicated	As clinically indicated, or at any time when recurrence is suspected							
Cardiac assessments											
Single ECG (standard 12-lead)	D	7.2.2.6	X		X	X		X	X (at C7D1 for all patients, then assessed only if QTcF $\geq$ 481 msec during previous cycles)	X	
Safety											
Adverse events	D	8	Continuous, up to 30 days after last dose of ribociclib								

	Category	Protocol Section	Screening phase	Treatment phase Ribociclib + endocrine therapy (26 cycles / approx. 24 months)							
Visit Name			**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3 to 6**	**Cycles 7 to 26 (every 3 cycles from C7D1)**	**End of treatment**	**Safety follow up**
Study/treatment cycle day			**-28 to -1**	**1**	**15**	**1**	**15**	**1**	**1**	**Within 15 days from last dose of ribociclib**	**Last dose of ribociclib + 30 days**
Study Drug administration											
Ribociclib	D	6		Day 1-21 daily, Day 22-28 off							
Adjuvant endocrine therapy (ET)	D	6	letrozole / anastrozole / exemestane daily, GnRH agonist (if indicated) every 4 weeks								
Discontinuation											
IRT Discontinuation ribociclib	S	7.1.3								X	
Subsequent anti-neoplastic therapies (medication, surgery, radiotherapy)	D	7.1.5								X	

7.1.1 Screening

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

Re-screening of patients is only allowed **once** per patient if the patient was not registered as entering the treatment phase before (i.e. IRT randomization). In this case the Subject Number assigned to the patient initially will be used and the patient will be identified with this number throughout his/her entire participation to the study. If patient has been randomized, re-screening of patient is not allowed.

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, AEs and medical history will be assessed relative to the new informed consent date.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range before screen failing the patient. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. For details of assessments, see Table 7-1.

A mandatory archival paraffin tumor tissue (tumor blocks or slides with tumor tissue) from surgical specimen should be shipped to the designated laboratory before the planned randomization date (see Section 7.2.3.1.1).

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

Any imaging assessments, if clinically indicated, are to be done during Screening period (i.e. within 28 days prior to randomization).

An additional biomarkers informed consent will be available to the patient for optional participation.

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 randomized 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, Inclusion/Exclusion pages and, if applicable, withdrawal of informed consent 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 an SAE during the Screening Phase (see Section 8 for SAE reporting details).

If a screen failure patient experiences an AE which does not meet the SAE criteria, details about the AE will be recorded only in the investigator's source documents. In case of an SAE after signing of main study informed consent, data must be recorded on both the AE and SAE forms.

If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

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 or partial date of birth and initials (where permitted by local regulations), sex, race, ethnicity).
- 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 per CTCAE v 4.03.
- ER, PgR, HER2, histopathological grade (the Nottingham combined histologic grade (Elston and Ellis 2002)) and, if available, Ki-67, genomic subtype and results of any of the genomic predictive and prognostic tests.
- Diagnosis and extent of cancer (including histology and AJCC 8th edition Anatomic ("TNM staging") and Prognostic Stage Groups (see Table 14-1 and Table 14-2 in Appendix 1):
  - Anatomic Stage Group at time of diagnosis, i.e. before the curative surgery, if available
  - Anatomic and Prognostic Stage Groups at the study entry, i.e. after the curative surgery:
    - for patients who received adjuvant chemotherapy reporting of both Anatomical Stage Group and Prognostic Stage Group is required
    - for patients who received neoadjuvant chemotherapy reporting of Prognostic Stage Group is not required.
- All prior anti-neoplastic therapies including surgical interventions, and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for the current early breast cancer as well as any adjuvant ET started prior to the randomization (ovarian suppression for fertility preservation by GnRH agonists is not considered anti-neoplastic therapy).
- 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, EORTC QLQ-BR23 (for women only), EQ-5D-5L, and HADS (See Section 7.2.5).

Furthermore the following assessments will be performed:

- Vital signs
- Height, weight
- Physical examination
- ECOG Performance Status
- Menopausal status (for women)
- Laboratory evaluations (hematology, coagulation, chemistry, urinalysis, pregnancy test for women of child bearing potential)
- Triplicate ECG
- Clinical evaluation for recurrence and if clinically indicated, radiological and/or histological/cytological assessments.
- A mandatory archival paraffin tumor tissue (tumor block or tumor slides with tumor tissue) from surgical specimen.

7.1.2 Treatment period

Patients will be randomized using menopausal status, stage group (i.e., Prognostic Stage Groups (see Table 14-2 in Appendix 1) for patients who were treated with adjuvant chemotherapy, or patients with residual disease in lymph nodes and breast tissue after neoadjuvant chemotherapy) and geographical region for stratification. Study treatment should be started as soon as possible and no later than 3 days after the randomization of the patient.

The study has been closed to enrollment. All randomized patients were unblinded; patients randomized to placebo permanently discontinued study treatment and patients randomized to ribociclib were offered the option to continue treatment with ribociclib + ET (excluding tamoxifen) for a maximum of 26 cycles (approximately 24 months) of ribociclib or until first recurrence, intolerable 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, whichever is earlier. Treatment ends with the last dose of ribociclib.

For details of assessments, see 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 a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate 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, he/she believes that continuation would be detrimental to the patient's well-being.

In addition to mandatory discontinuation reasons for investigational treatment (ribociclib) listed in Section 6.2, study treatment **must** also be discontinued under the following circumstances:

- Pregnancy
- Lactation
- Death
- Subject/Guardian decision
- Adjustments to study treatment due to toxicity that result in treatment discontinuation (see Section 6.2)
- Use of prohibited medication (see Section 6.3).
- Any other protocol deviation that results in a significant risk to the patient's safety.

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 7.2 for an EOT visit. 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 7.1.6.

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

Patients who discontinue study treatment should undergo an End of Treatment (EOT) visit followed by a 30 day safety follow-up. At EOT visit, all the assessments as listed in Table 7-1 will be performed. If the decision to discontinue the patient occurs at a regularly scheduled visit, that visit may serve as the EOT visit rather than having the patient return for an additional visit.

7.1.3.1 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 should make a reasonable effort (e.g. telephone, e-mail, letter) to understand 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.

7.1.4 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of ribociclib. Once an AE is detected, investigators are required to follow this AE until its resolution or stabilization. Refer to Section 8.1.1 for definitions and reporting of AEs. 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.

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

7.1.5 Follow-up phase

7.1.5.1 Post treatment follow up for recurrence

Since the study will end after the completion of safety follow up within 30 days after the last dose of ribociclib, no post-treatment follow-up for recurrence will be conducted. Patients in post-treatment follow-up phase assessments will end study participation with the protocol amendment 02.

7.1.5.2 Survival follow-up

Since the study will end after the completion of safety follow-up assessment within 30 days after the last dose of ribociclib, no survival follow up will be conducted. Patients in survival follow-up phase assessments will end study participation with the protocol amendment 02.

7.1.6 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 CRF.

7.2 Assessment types

7.2.1 Recurrence assessments

Recurrence will be assessed by investigator according to local or institutional standards of care, as clinically indicated, or at any time when recurrence is suspected.

Any of the following radiological assessments may be used for evaluation of suspicion of recurrence:

- Chest, abdomen and pelvis computer tomography (CT) or magnetic resonance imaging (MRI)
- Brain CT or MRI
- Whole body bone scan (bone scintigraphy)
- Localized bone CT, MRI or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- CT or MRI of other sites (e.g., neck, extremities)
- Ultrasound
- Fludeoxyglucose (^{18}F) positron emission tomography (FDG-PET)
- Mammography

Biopsy or cytology maybe used to confirm recurrence histologically (or cytologically), unless the biopsy poses an unacceptable risk to the patient. Recurrence will be reported in eCRF. Treatment with ribociclib + ET will be discontinued at time of recurrence (any type of recurrence - either local, regional, distant, contralateral non-invasive breast cancers or second-primary invasive non-breast cancer).

7.2.2 Safety and tolerability assessments

Safety of patients will be monitored by assessing physical examinations, height and weight, vital signs, ECG, laboratory assessments including hematology, chemistry, and coagulation as well as collecting of the AEs at every visit. For details on AE collection and reporting, see Section 8.

The ECOG Performance Status and patient-reported outcomes are no longer collected following the protocol amendment 02.

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 will be measured at screening only.

Weight will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.4 Performance status

Following the protocol amendment 02, the performance status assessment is no longer performed.

7.2.2.5 Laboratory evaluations

Following the protocol amendment 02, all clinical laboratory analyses (Hematology, Chemistry, Coagulation, Urinalysis, and serum pregnancy test) will be performed by the local laboratory only (see Table 7-3). The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used (except for FSH and estradiol for determination / confirmation of menopausal status).

Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) AE.

At any time during the study up to safety follow-up, 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. The severity of laboratory data will be graded using the Common Terminology Criteria for Adverse events (CTCAE) version 4.03. Additional analyses are left to the discretion of the investigator.

Table 7-2 Clinical laboratory parameters collection plan (all are done locally with the protocol amendment 02)

Test Category	Test Name
Hematology	White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), bands, differential other, hemoglobin and platelet count
Biochemistry	Sodium, potassium, uric acid, urea or BUN, creatinine, glucose (fasting only if non-fasting is out of range), calcium, magnesium, phosphorous and albumin. AST (SGOT), ALT (SGPT), total bilirubin, direct bilirubin and alkaline phosphatase, Amylase, lipase and LDH, total cholesterol
Coagulation	aPTT, 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)
Other Tests	Pregnancy test (serum)

7.2.2.5.1 Hematology

Hematology tests are to be performed according to the Visit Schedule outlined in Table 7-1. For details of the Hematology panel see Table 7-2.

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

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 see Table 7-2. Biochemistry should be assessed on the actual scheduled day, even if study drug is being withheld. Estimate of GFR (via estimated creatinine clearance rate) will be done centrally using Cockcroft-Gault formula

Estimated creatinine clearance rate (eC_{Cr}) using Cockcroft-Gault formula

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

7.2.2.5.3 Coagulation

INR and aPTT are to be performed according to the Visit Schedules outlined in Table 7-1. 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 laboratory INR test ≤ 1.5.

Coagulation will be performed by local laboratory following the protocol amendment 02.

7.2.2.5.4 Urinalysis

Urinalysis is to be performed according to the Visit Schedules outlined in Table 7-1. For details of the urinalysis panel see Table 7-2.

7.2.2.5.5 Pregnancy and assessments of fertility

FSH, estradiol, serum and urine pregnancy tests (patients who have undergone a hysterectomy do not need pregnancy tests performed) are to be performed according to the Visit Schedules outlined in Table 7-1 and Table 7-3.

At screening and at EOT, a serum pregnancy test should be performed for women of child bearing potential only, while at Cycle 1 day 1 and at each cycle, urinary pregnancy tests are sufficient.

FSH and estradiol will be done locally at screening for eligibility and for confirmation of the menopausal status. Menopausal status will be recorded in eCRF.

Table 7-3 Local clinical laboratory parameters assessment plan

Test Category	Test Name
Other local Tests	FSH, estradiol for confirmation of menopausal status (pre- / post-), urine pregnancy. Note: FSH and estradiol are not recorded in eCRF, but used to determine menopausal status

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard single 12 lead ECG assessments will be performed (in the supine position) after the patient has been resting for 5-10 minutes prior to each time point indicated in Table 7-4 below. ECG assessments are to be done prior to blood collection sampling (if applicable). Following the protocol amendment 02, all ECG will be performed and assessed locally.

Table 7-4 ECG collection plan (all ECGs are performed and assessed locally with the protocol amendment 02)

Cycle	Patients	Day	Time	ECG Type
Screening	All	-28 to -1	Anytime	Triplicate 12 Lead
1	All	Day 15	Pre-dose[1]	Single 12 Lead
	All		2h post-dose (± 15 min)	Single 12 Lead
2	All	Day 1	Pre-dose[1]	Single12 Lead
3	All	Day 1	Pre-dose[1]	Single 12 Lead
4	All	Day 1	Pre-dose[1]	Single 12 Lead
5	All	Day 1	Pre-dose[1]	Single 12 Lead
6	All	Day 1	Pre-dose[1]	Single 12 Lead
7	All	Day 1	Pre-dose[1]	Single 12 Lead
10 and every 3rd cycle	For patients with QTcF ≥ 481 msec at any time prior to cycle 7	Day 1	Pre-dose[1]	Single 12 Lead
EOT			Anytime	Single 12 Lead
Unscheduled ECG			Anytime	Single 12 Lead
[1]The exact date and time of dosing must be recorded on the appropriate eCRF				

The QTcF values using Fridericia's correction (formula is provided below) will be assessed locally following the protocol amendment 02.

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Eligibility will be based on the average of the triplicate ECGs conducted at screening.

If any of the readings include a new clinically-relevant abnormal ECG or a QTcF value of ≥ 481 msec is obtained at any time after randomization, study treatment must be interrupted, repeat ECG and follow management guidelines detailed in Table 6-5.

An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Local cardiologist ECG assessment may be performed at any time during the study at the discretion of the investigator.

All ECGs including unscheduled ECGs with clinically relevant findings, collected during the study should be assessed locally. Each ECG tracing should be labeled with the study number, patient number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening when the patient signed informed consent should be reported on the Medical History CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.3 Biomarkers

Following the protocol amendment 02, tumor and blood samples collection for biomarkers assessments are no longer performed.

7.2.4 Resource utilization

Following the protocol amendment 02, collection of data for healthcare resource utilization is no longer performed.

7.2.5 Patient reported outcomes

Following the protocol amendment 02, collection of data for patients reported outcomes is no longer performed.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event (AE) 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 AEs 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 treatment(s).

AEs 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. AE monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. AEs (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 AE.

AE will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will

be used. Information about any deaths (related to an AE or not) will also be collected through a Death form.

The occurrence of AEs 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. AE 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 AE should be evaluated to determine:

- The severity grade (CTCAE v4.03 Grades 1-5)
- Its duration (Start and end dates)
- Its relationship to the study treatment. Reasonable possibility that AE is related:
  - No (i.e. not treatment-related);
  - Yes, investigational treatment (i.e. related to treatment with ribociclib);
  - Yes, other study treatment (i.e. related to treatment with ET);
  - Yes, both and/or indistinguishable (i.e. related to treatment with both ribociclib and ET, or indistinguishable)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Whether it is serious, where an SAE is defined as in Section 8.2.1 and which seriousness criteria have been met
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For all AEs, 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 previous grade.

All AEs 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 AE 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.

Recurrence of malignancy (including resulting in fatal outcomes), if documented by use of appropriate method (for example, confirmed recurrence per STEEP Criteria is reported), should not be reported as an AE, including SAE.

AEs 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 AE 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 AEs 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 AE, 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 AE, should not be reported as AEs. 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 of medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an AE and must be reported as such.

8.1.3 Adverse events of special interest

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

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

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 SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.

- Social reasons and respite care in the absence of any deterioration in the patient's general condition.

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 an SAE.

8.2.2 Reporting

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

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. 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.

Any SAEs experienced after the 30 day safety evaluation follow-up period should be reported to Novartis within 24 hours of learning of its occurrence if the investigator suspects a causal relationship to the study treatment.

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

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

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

8.3 Emergency unblinding of treatment assignment

This is not applicable since all patients have been unblinded.

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 any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

8.5 Warnings and precautions

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

The study enrollment was early closed. All randomized patients were unblinded. After the unblinding, the Novartis Clinical Trial Team will be responsible for reviewing safety data and conducting all analysis(-es) as defined in the protocol.

8.7 Steering Committee

Following the protocol amendment 02, this section is no longer applicable.

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

Following the protocol amendment 02, laboratory and ECG data will be collected and performed locally at the sites; data will be entered into the eCRF. PRO data will not be collected any longer. Blood and tumor samples for laboratory data and biomarker assessments will no longer be collected.

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

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

Samples and/or data (e.g. biomarkers, ECG, safety samples) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). 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).

Following the protocol amendment 02, PRO data will not be recorded as this assessment is no longer required. Blood and tumor samples for laboratory data and biomarker assessments will no longer be collected. 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 (or designated CRO).

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

The final analysis will be performed after all patients have discontinued ribociclib and the safety follow-up assessment within 30 days after the last dose of ribociclib.

No analyses for statistical inference is planned. Descriptive summaries of key safety and baseline characteristics will be provided. These include summaries of treatment duration exposure, adverse events, labs, and ECG findings. The efficacy data collected will be summarized via listings. The details are described in the statistical analysis plan.

10.1 Interim analysis

Not applicable

10.2 Sample size calculation

Not applicable

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

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

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

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

Additional consent form

Sub-studies and studies with an optional Exploratory Biomarker component will have a separate consent form covering those studies (See Section 7.2.3.3.1 for pharmacogenetic informed consent details). This form will be adapted for each Study based on a standard template used globally for all Studies. These informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a subject opts not to participate in the optional assessments, this in no way affects the subject's ability to participate in the main research study.

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study

start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., last patient last visit (LPLV)), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

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

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

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

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

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of 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 Novartis 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.

13 References (available upon request)

Amin MB (2016) AJCC Cancer Staging System, 8th Edition: UPDATE. Creating the Bridge from a “Population Based” to a More “Personalized” Approach. https://cancerstaging.org/About/news/Documents/NCRA%20AJCC%20Cancer%20Staging%20Manual%208th%20Edition%20Update.pdf Accessed on 07-Nov-2016.

Anampa J, Makover D, Sparano JA (2015) Progress in adjuvant chemotherapy for breast cancer: an overview. BMC Medicine 13:195.

Bachelot T, Bourgier C, Cropet C, et al (2012) Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol 30:2718–2724.

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

Bosco EE, Wang Y, Xu H, et al (2007) The retinoblastoma tumor suppressor modifies the therapeutic response of breast cancer. J Clin Invest 117:218-228.

Buzdar AU (2003) Pharmacology and pharmacokinetics of the newer generation aromatase inhibitors. Clin Cancer Res. 9:468S-472S.

Coates AS, Winer EP, Goldhirsch A, et al (2015). Tailoring therapies – improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 26:1533-1546

Dawson SJ, Rosenfeld N, Caldas C. (2013) Circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med. 369(1):93-4.

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717.

Early Breast Cancer Trialists’ Collaborative Group (2015) Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 386:1341–1352.

Edevana VK, Dhakal IB, Williams S, et al (2013) Potential role of UGT1A4 promoter SNPs in anastrozole pharmacogenomics. Drug and Metabolism Dispos 41:870-877.

Eggeman H, Ignatov A, Smith BJ, et al (2013) Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat 137:465–470.

Elston, CW, and Ellis, IO (2002) Pathologic prognostic factors in breast cancer. I. The value of histological grades in breast cancer. Experience from a large study with long-term follow-up". Histopathology. 1991;19: 403–10. Republished in Histopathology 41:154–161.

Esposito A, Bardelli A, Criscitiello C, et al (2014) Monitoring tumor-derived cell-free DNA in patients with solid tumors: clinical perspectives and research opportunities. Cancer Treat Rev; 40(5):648-55.

Fentiman IS, Fourquet A, Hortobagyi GN (2006) Male breast cancer. Lancet 367:595–604.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al (2013). Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 49:1374-1403

Finn RS, Dering J, Conklin D, et al (2009) PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Can Res 11:R77.

Finn RS, Crown JP, Lang I, et al (2015) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study Lancet Oncol 16:25–35.

Finn RS, Martin M, Rugo HS, et al (2016) Palbociclib and letrozole in advanced breast cancer. NEJM 375:1925-1936.

Francis PA, Regan MM, Fleming GF, et al (2015). Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 372:436-446.

Giuliano AE, Hunt KK, Ballman KV, et al (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305:569-575.

GLOBOCAN (2012) Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (assessed 17-October-2016).

Goetz MP, Erlichman C, Loprinzi CL, and Kohli M (2015) Hormonal agents. In DeVita VT, Lawrence TS, and Rosenberg SA "DeVita, Hellman, and Rosenberg's Cancer: principles & practice of oncology". 10th edition. Wolters Kluwer Health.

Goss PE, Ingle JN, Pritchard KI, et al (2016) Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 375:209-219.

Gradishar WJ, Anderson BO, Balassanian R, et al (2016) Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 14:324-354.

Grunberg SM, Warr D, Gralla RJ, et al (2010) Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity- state of the art. Support Care Cancer 19:S43-S47.

Hammond ME, Hayes DF, Dowsett M, et al (2010) American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28:2784–2795.

Holm K, Staaf J, Jönsson G, et al (2012) Characterisation of amplification patterns and target genes at chromosome 11q13 in CCND1-amplified sporadic and familial breast tumours. Breast Cancer Res Treat 133:583-594.

Hortobagyi GN, Connolly JL, D'Orsi CJ, et al (2017). Breast. From AJCC Cancer Staging Manual 8th ed. By Amin MB, Edge S, Greene FL, et al. Springer

Hortobagyi GN, Stemmer SM, Burris HA, et al (2016) Ribociclib as first-line therapy for HR-positive, advanced Breast Cancer. N Engl J Med 375:1738-1748.

Hoskins JM, Carey LA, McLeod HL (2009) CYP2D6 and tamoxifen: DNAA matters in breast cancer. Nat Rev Cancer 9:576-586.

Howlander N, Noone AM, Krapcho M, et al (2015) SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.

Jemal A, Center MM, DeSantis C, and Ward EM (2010) Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 19:1893–1907.

Jeruss JS, Mittendorf EA, Tucker SL, et al (2008) Combined use of clinical and pathologic staging variables to define outcomes for breast cancer patients treated with neoadjuvant therapy. J Clin Oncol 26:246-252.

Lan KK, DeMets DL (1983). Discrete sequential boundaries for clinical trials. Biometrika; 70:659-63.

Lipton A, Demers LM, Harvey HA, et al (1995) Letrozole (CGS 20267). A phase I study of a new potent oral aromatase inhibitor of breast cancer. Cancer. 75:2132-2138

Loibl S, Turner NC, Ro J, et al (2016) Palbociclib (PAL) in combination with fulvestrant (F) in pre-/peri-menopausal (PreM) women with metastatic breast cancer (MBC) and prior progression on endocrine therapy – results from Paloma-3. J Clin Oncol 34 (suppl; abstr 524)

Lyman GH, Temin S, Edge SB, et al (2016) Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical Practice Guideline update. J Clin Oncol 32:1365-1383.

Mauri D, Pavlidis N, and Ioannidis (2005) Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. JNCI J Natl Cancer Inst 97:188-194.

Miller TW, Balko JM, Fox EM, et al (2011) ERα-dependent E2F transcription can mediate resistance to estrogen deprivation in human breast cancer. Cancer Discov 1:338-351.

von Minckwitz G, Untch M, Blohmer JU et al (2012) Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes J Clin Oncol. 30(15):1796-804.

Mittendorf EA, Jeruss JS and Tucker SL (2011) Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol 15:1858-1882.

Murtaza M, Dawson SJ, Pogrebniak K et al (2015) Multifocal clonal evolution characterized using circulating tumour DNA in a case of metastatic breast cancer. Nat Commun. 6:8760.

Musgrove EA, Caldon CE, Barraclough J, et al (2011) Cyclin D as a therapeutic target in cancer. Nat Rev Cancer 11:558-572.

NCCN Clinical Practice Guidelines in Oncology. Antiemesis. Version 2.2016 https://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf

Nichols M (2015) New directions for drug-resistant breast cancer: the CDK4/6 inhibitors. Future Med Chem 12:1473-1481.

Plourde PV, Dyroff M, Dowsett M, et al (1995) Arimidex: A new oral, once-a-day aromatase inhibitor. J Steroid Biochem Molec Biol 53:175-199.

Rizzo JD, Brouwers M, Hurley P, et al (2010) American Society of Clinical Oncology/ American Society of Hematology Clinical Practice Guideline update on the use of epoetin and darbepoetin in adult patients with cancer J Clin Oncol 33:4996-5010

Roila F, Molassiotis A, Herrstedt J, et al (2016) MASCC and ESMO Consensus Guidelines for the Prevention of Chemotherapy and Radiotherapy-Induced Nausea and Vomiting: ESMO Clinical Practice Guidelines. Ann Onc 27:v11-v133.

Senkus E, Kyriakides, S, Ohno S, et al (2015) Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26 (suppl 5): v8-v30.

Siegel RL, Miller KD, Jemal (2016) A Cancer statistics, 2016. CA Cancer J Clin 66:7-30.

Smith TJ, Bohlke K, Lyman GH, et al (2015) Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33:3199-3212

Sousa B, Moser E, and Cardoso F (2013) An update on male breast cancer and future directions for research and treatment. Eur J Pharmacol 71:771–783.

Thangavel C, Dean JL, Ertel A, et al (2011) Therapeutically activating RB: reestablishing cell cycle control in endocrine therapy-resistant breast cancer. Endocr Relat Cancer 18:333-345.

The Cancer Genome Atlas Network (2012) Comprehensive molecular portraits of human breast tumours. Nature 490:61-70.

Torre LA, Bray F, Siegel RL et al (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108.

Tripathy D, Sohn J, Im SA, et al (2017). First-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: results from the randomized phase III MONALEESA-7 trial. Presented at: the 2017 San Antonio Breast Cancer Symposium; Abstract GS2-05.

Trunet PF, Bhatnagar AS, Chaudri HA, et al (1996) Letrozole (CGS20267) a new oral aromatase inhibitor for the treatment of advanced breast cancer in postmenopausal patients. Acta Oncol 35S5:15-18

Turner NC, Ro K, Andre F (2015) Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 373:209-219.

14 Appendices

14.1 Appendix 1: Guidelines for Anatomic and Prognostic Stage Group III of HR-positive, HER2-negative Breast Cancer for breast cancer staging (based on AJCC Ed. 8th)

Guidelines for anatomic and prognostic stage groups according to AJCC Ed. 8th applicable to this study are presented in Table 14-1 and Table 14-2 below (modified from Hortobagyi et al 2017).

Table 14-1 AJCC 8th edition Anatomic Stage Groups (not including Group IV - all M-category M0)

Anatomic Stage Group	T-category	N-category
0	Tis	N0
IA	T1	N0
IB	T0-1	N1mi
IIA	T0-1	N1
	T2	N0
IIB	T2	N1
	T3	N0
IIIA	T0-3	N2
	T3	N1
IIIB	T4	N0-2
IIIC	Any T	N3

Table 14-2 AJCC 8th edition Prognostic Stage Group III of HR-positive, HER2-negative Breast Cancer (all M-category M0)

T-category	N-category	Grade	ER Status	PR Status
Prognostic Stage Group IIIA				
T0-1	N1	3	Positive	Negative
T0-1	N1	3	Negative	Positive
T2*	N0	3	Positive	Negative
T2	N0	3	Negative	Positive
T2	N1	1 or 2	Positive	Negative
T3	N0	1 or 2	Positive	Negative
T0-2	N2	1	Positive	Negative
T0-2	N2	1	Negative	Positive
T3	N1-2	1	Positive	Negative
T3	N1-2	1	Negative	Positive
T4	N0-2	1	Positive	Positive
Any	N3	1	Positive	Positive

T-category	N-category	Grade	ER Status	PR Status
Prognostic Stage Group IIIB				
T2	N1	3	Positive	Negative
T3	N0	3	Positive	Negative
T0-2	N2	2	Positive	Negative
T0-2	N2	2	Negative	Positive
T0-2	N2	3	Positive	Positive
T3	N1-2	2	Positive	Negative
T3	N1-2	2	Negative	Positive
T3	N1-2	3	Positive	Positive
T4	N0-2	2	Positive	Positive
Any	N3	2	Positive	Positive
Prognostic Stage Group IIIC				
T2	N1	3	Negative	Positive
T3	N0	3	Negative	Positive
T0-2	N2	3	Positive	Negative
T0-2	N2	3	Negative	Positive
T3	N1-2	3	Positive	Negative
T3	N1-2	3	Negative	Positive
T4	N0-2	1 or 2 or 3	Positive	Negative
T4	N0-2	1 or 2 or 3	Negative	Positive
T4	N0-2	3	Positive	Positive
Any	N3	1 or 2 or 3	Positive	Negative
Any	N3	1 or 2 or 3	Negative	Positive
Any	N3	3	Positive	Positive

*If Oncotype Dx® was performed and the recurrence score is less than 11, then T1-2, N0, grade 1-3 patients would be considered to be Prognostic Group IA

14.2 Appendix 2: Concomitant medications

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

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction and Co-Medication Considerations (v06 release date: 2016), 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 14-3 List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	VIEKIRA PAK2, indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat (GS-9350), indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, saquinavir, idelalisib, boceprevir, darunavir/ritonavir
Strong CYP3A4/5 inducers	Avasimibe[2,3], carbamazepine, enzalutamide, 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, lomitapide
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, procainamide, propofol, quinidine, sevoflurane, sotalol, sulpiride, terfenadine, thioridazine, vandetanib
Herbal preparations/ medications	Herbal preparations/medications known as strong inducers or inhibitors of CYP3A4/5 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 anti-neoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anti-neoplastic 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 treatment. If such agents are required for a patient then the patient must discontinue study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[2] Herbal product
[3] P-gp inducer
[4] Source: qtdrugs.org (as of March 2, 2018)
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 14-4 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 netupitant, tofisopam, verapamil, crizotinib, faldaprevir, imatinib, nilotinib
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, lersivirine, modafinil, nafcillin, talviraline, semagacestat, lopinavir
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, alisoporivir, almorexant, aplaviroc, apixaban (doses < 2.5 mg only), atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, danoprevir,darifenacin, darunavir, dasatinib, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, ibrutinib, ivacaftor, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, vicriviroc, voclosporin
Strong BSEP inhibitors	Alectinib, atazanavir, bromocriptine, Bosentan, clofaziminie, cerivastatin, fusidate, glibenclamide, glyburide, nefazadone, paritaprevir, pioglitazone, reserpine, rosiglitazone, sulindac, troglitazone (TGZ-sulfate), valinomycin
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine, atazanavir, atomoxetine, asenapine, bedaquiline, bortezomib, buprenorphine, capecitabine, ceritinib, clomipramine, crizotinib, clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, eribulin, ezogabine, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisertron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, lapatinib, lenvatinib, leuprolide, loperamide, lithium, metolazone, mifepristone, mirabegron, mirtazapine, moexipril, norfloxacin, nortriptyline, ofloxacin, olanzapine, osimertinib, ondansetron (p.o. only at 4 mg or 8 mg), oxytocin, paliperidone, panabinostat, pasireotide, pazopanib, pipamperone, promethazine, propafenone, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, sorafenib, sunitinib, telavancin, tetrabenazine, tizanidine, tolterodine, toremifene, tramadol, trimipramine, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1 and OCT2 substrates[3]	Acyclovir, amantadine, amiloride, apricitabine, carboplatin, cisplatin, cephalexin, cephradine, cimetidine, dofetilde, famotidine, fexofenadine, furamidine, ganciclovir, glycopyrronium, Ipratropium, lamivudine, linagliptin, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), oxyplatin, pindolol, plisicainide, pramsorafenib, ranitidine, topotecan, tropisetron, trospium, umeclidinium, varencicline, zidovudine

Category	Drug Name
BCRP substrates	Daunorubicin, doxorubicin, ethinyl estradiol methotrexate, mitoxantrone, pitavastatin, rosuvastatin, sulfasalazine, sofosbuvir, tenofovir

[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 March 02,, 2018)
[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; www.druginteractioninfo.org (as of May, 2016)