Clinical Development

LEE011/Ribociclib/Kisqali®

CLEE011A2207 / NCT03822468

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

Statistical Analysis Plan (SAP)
Amendment 2

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14-May-2019	Prior to DB lock	Creation of final version	N/A - First version	NA
11-Jan-2021	Prior to DB lock	Considerations of COVID-19 impact on analyses	New protocol deviations resulting from COVID-19 pandemic and corresponding detailed relationship have been defined and will be summarized. Baseline demographic characteristics, diagnosis and extent of cancer, and prior anti-neoplastic therapy will be summarized for patients randomized before and after the start of the pandemic.	Section 2.2.3 and Section 2.5.6
02-Aug-2021	Prior to DB lock	Exclude protocol deviaition "patients dose reduced in the first cycle". Change ORR 95% CI calculation method due to small smaple in some subgroups. Child bear status was not collected in the CRF.	Dose reduction in the first cycle was changed to a condition to exclude the subject from PPS not a protocol deviation. Child bearing status was removed from listing. For subgroup analysis, the 95% CI will be calculated by exact method. The best response to last prior antineoplastic therapy will not be summarized due to most responses is unkown, missing or not applicable.	Section 2.2.1, Section 2.2.5, Section 2.2.6, Section 2.5.5

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List of abbreviations

aBC	advanced breast cancer
AE	Adverse event
AI	aromatase inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BC	breast cancer
BOR	Best overall response
CBR	Clinical benefit rate
CR	Complete response
CRS	Case retrieval strategy
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ΔQTcF	Change from baseline in QTcF
DMC	Data Monitoring Committee
DOR	Duration of Response
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FAS	Full analysis set
HER2	Human epidermal growth factor receptor 2
HR	Hazard Ratio
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
NI	Non-inferiority
NMQ	Novartis MedDRA queries
NSAI	Non-steroidal aromatase inhibitor
ORR	Overall response rate
PAS	Pharmacokinetic analysis set
PD	Progressive disease
PDI	Planned dose intensity
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics

PPS	Per-Protocol Set
PR	Partial response
PT	Preferred term
qd	Qua'que di'e / once a day
QTcF	QT interval corrected by Fridericia method
RAP	Report and Analysis Process
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SEC	Safety Event Categories
SMQ	Standardized MedDRA queries
SOC	System Organ Class
TA	Tumor assessment
TBIL	Total Bilirubin
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, Listings
WHO	World Health Organization
UNK	Unknown

1 Introduction

This document describes the detailed statistical methodology to be used for the clinical study report (CSR) for the primary analysis of study CLEE011A2207, a phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of 400 mg of ribociclib in combination with non-steroidal aromatase inhibitors (NSAI) for the treatment of pre- and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer (aBC) who received no prior therapy for advanced disease.

The content of this SAP is based on the CLEE011A2207 protocol amendment 1 released on Jan 24, 2020. All decisions regarding final analysis, as defined in this document, have been made prior to the database lock.

CSR deliverables (shells for tables, figures, listings) and further programming specifications are described in the Tables, Figures & Listings (TFL) shells and Programming Datasets Specification (PDS), respectively.

1.1 Study design

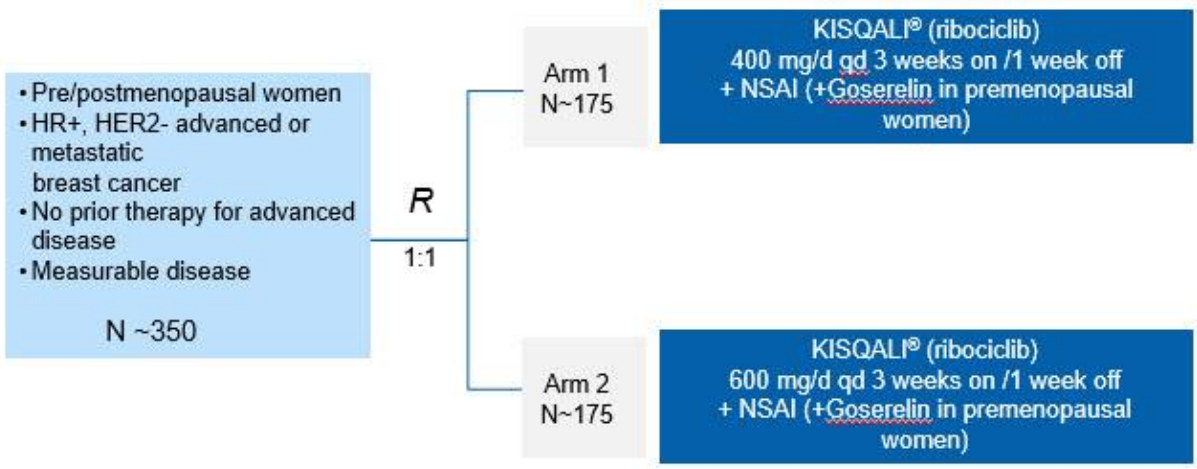
This is a phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of a reduced starting ribociclib dose of 400 mg in combination with an NSAI (letrozole or anastrozole) for the treatment of pre- and postmenopausal women with HR-positive, HER2-negative aBC who have received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

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

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

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

Figure 1-1 Study Design



The primary efficacy and safety analyses will be performed after all patients have been treated

for at least 6 months or have discontinued study treatment. Any additional data for patients continuing to receive study treatment past this time and for patients continuing for efficacy follow up (PFS), as allowed by the protocol, will be further summarized in a final study report at the end of the study. No formal interim analysis is planned for this study.

1.2 Study objectives and endpoints

The study objectives and corresponding endpoints as specified in the protocol are provided in Table 1-1.

Table 1-1 Objectives and related endpoints

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

2 Statistical methods

2.1 Data analysis general information

Novartis will perform the primary analyses and produce statistical outputs using SAS 9.4 or later version.

The primary efficacy and safety analyses will be performed after all patients have been treated for at least 6 months or have discontinued study treatment, and the corresponding on-treatment

scans have been collected. On-treatment scan refers to the scan taken within 30 days after the last dose of study treatment. The cut-off will accommodate the timing to perform any additional scan required to confirm the CR and PR per RECIST 1.1, even if that scan may be scheduled after 6 months, and will also take into account the time window of ± 1 week for the tumor scan as allowed by the protocol.

Statistical analyses will be performed using all data collected in the database up to the data cut-off date. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

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

2.1.1 General definitions

2.1.1.1 Study drug and study treatment

Study drug is defined as ribociclib either 600mg or 400mg.

Study treatment is defined as ribociclib 600mg + NSAI ± goserelin, or ribociclib 400mg + NSAI ± goserelin.

2.1.1.2 Date of first administration of study drug

The date of first administration of study drug is defined as the first date when a nonzero dose of study drug is administered and recorded on the dose administration DAR CRF. The date of first administration of study drug will also be referred to as start of study drug. Similar definitions apply for the other components of study treatment.

2.1.1.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered and recorded on the DAR CRF date. Similar definitions apply for the other components of study treatment.

2.1.1.4 Date of first administration of study treatment

The date of first administration of study treatment is defined as the first date when a nonzero dose of any component of study treatment is administered and recorded on the DAR CRF. The date of first administration of study treatment will also be referred to as the start of study treatment.

2.1.1.5 Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of any component of study treatment was administered and recorded on the DAR CRF.

2.1.1.6 Study day

The study day will be calculated as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) is the start of study treatment. (Note: if an adverse event starts before the start of study treatment, the study day displayed on the listing will be negative).

The reference start date for all other, non-safety assessments (i.e., tumor assessment, death, disease progression, tumor response and ECOG performance status) is the date of randomization. In other words, all efficacy time-to-event variables (e.g. progression-free survival, time to response) will be calculated from date of randomization. (Example: if randomization date is 15DEC2018, start of study drug is on 18DEC2018, and the date of death is 28DEC2018 then the study day when the death occurred is 14).

The study day will be displayed in data listings.

2.1.1.7 Baseline

For efficacy evaluations, the last available assessment on or before the date of randomization will be used as the “baseline” value or “baseline” assessment. In the context of baseline definition, the efficacy evaluations also include ECOG performance status. For RECIST-based endpoints (e.g. best overall response and PFS), a window of 7 days after the start of study treatment will be allowed, i.e. the baseline will also be considered valid if it occurs within +/-7 days of the treatment start date.

For safety evaluations (e.g. laboratory assessments and ECG), the last available assessment before or at date of start of study treatment will be used as the ‘baseline’ assessment. Assessments specified to be collected post-dose on the first date of treatment are not considered as baseline values.

If patients have no value as defined above, the baseline results will be considered missing.

2.1.1.8 On-treatment assessment/event

Safety summaries and selected summaries of deaths will summarize only on-treatment assessments/events. An on-treatment assessment/event is defined as any assessment/event in the following time interval: [date of first administration of study treatment, date of last administration of study treatment + 30 days], i.e. including the lower and upper limits. (Note: However, the calculation of study treatment duration will use different rules as specified in Section 2.6.1.1).

An AE starting in the screening phase and ongoing in the on-treatment phase will not be considered an on-treatment AE unless it has worsened.

If the last date of study treatment is missing, any assessment/event occurring after the start of study treatment will be considered as on-treatment.

Data listings will include all assessments/events, flagging those which are not on-treatment.

2.2 Analysis sets

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

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

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

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

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

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as

a. the randomized treatment if the patient took at least one dose of that treatment or
b. the first treatment received if the randomized treatment was never received.

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

2.2.1 Patient classification

Patients may be excluded from the analysis sets defined above based on the protocol deviations entered in the database and/or on specific subject classification rules as defined in Table 2-1.

Table 2-1 Patient classification based on protocol deviations and non-protocol déviations criteria

Analysis set	Protocol deviations leading to exclusion	Non-protocol deviation criteria leading to exclusion
FAS	No written informed consent	NA
Safety set	No written informed consent	No dose of study treatment
Per Protocol set	Any major protocol deviation as listed in definition of per protocol set	No dose of study treatment Patient had dose reduction of ribociclib within cycle 1

2.2.2 Withdrawal of informed consent

Any data collected in the clinical database after a patient withdraws informed consent from further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

2.2.3 Protocol deviation summaries

The number and percentage of patients in the FAS with any protocol deviations will be tabulated by deviation category (as specified in the Study Specification Document) and by treatment arm.

Protocol deviations leading to exclusion from PPS (Per Protocol Set) will be tabulated separately by treatment arm.

All protocol deviations, as well as protocol deviations leading to exclusion from the Per Protocol Set, will be listed.

In addition to the pre-defined standard protocol deviation terms, 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown, patient concerns, etc.) to the COVID-19 pandemic have been defined in alignment with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (December 2020) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (April 2020) from EMA as listed below.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Patient discontinuation due to COVID-19 situation

The number and percentage of patients with any protocol deviations in the FAS will be summarized by COVID-19 relationship (related or not-related) and by treatment arm in the post-text table. A cross-tabulation of COVID-19 related protocol deviation vs. corresponding detailed relationship will also be produced by treatment arm. The detailed relationship is listed as below:

- COVID-19 health status related
- COVID-19 situation: Site issue
- COVID-19 situation: Lockdown / Quarantine of patient
- COVID-19 situation: Patient concern
- COVID-19 situation: Drug supply issue
- COVID-19 situation: Other

2.2.4 Groupings for analysis

The number and percentage of patients in each analysis set will be summarized by treatment arm and randomization stratum.

2.2.5 Subgroup of interest

Subgroup analyses will be performed for efficacy as outlined below. The subgroup analyses will be performed in the PPS as well as in the FAS. Efficacy analyses in subgroups will be purely exploratory and are intended to explore the consistency of ORR in both arms. No inferential analysis that compares ORR between the two treatment arms will be performed within these subgroups.

Subgroups will be formed using CRF data. This includes variables related to the stratification factor (i.e. lung/liver metastases), and CRF data will be used to define these subgroups. Analyses by stratification factor based on IRT data are covered by the analyses described in Section 2.7.4.

For ORR, exploratory subgroup analyses will be performed using the following:

- Lung or liver involvement (Yes vs. No)
- Menopausal status (pre vs postmenopausal)
- Age group (< 40 vs ≥ 40 years, < 65 vs ≥ 65 years, < 75 vs ≥ 75 years)
- Race (Asian vs. non-Asian)
- Adjuvant or neo-adjuvant chemotherapy (Yes vs. No)
- Hormonal agent in (neo-)adjuvant setting (Yes vs. No)
- Region (Europe, North America and other)

For each of the subgroups, the following analyses will be performed:

ORR will be presented by treatment arm along with the two-sided exact binomial 95% confidence interval [Clopper and Pearson 1934].

2.3 Concomitant therapies with specific impact on the analysis

According to the study protocol, the following medications are prohibited while taking study treatment - ribociclib, NSAI, ± goserelin:

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

These substances are listed in Table 16-1 in the study protocol. A corresponding list for programming purposes will be saved in a separate document. If there is an update to the list of prohibited medications (e.g. protocol amendment), the most up-to-date list shall be used for the Clinical Study Report.

However, some patients may take these substances during the treatment period and these concomitant medications will be selected via programming and tabulated and listed in the Clinical Study Report. Treatment with the prohibited substances mentioned above will be identified in the database as protocol deviations.

With the exception of palliative radiotherapy, administration of anti-neoplastic therapies (apart from study treatment) is not allowed during study treatment. Patients who take anti-neoplastic therapies after randomization will be identified through data review. Tumor assessments (TAs) made after the start of anti-neoplastic therapies (whether on study treatment or afterwards) will not be included in the efficacy analyses based on best overall response (i.e. Overall Response Rate (ORR), Clinical Benefit Rate (CBR), time to response, and duration of response) and time to event analysis of PFS.

2.4 Implementation of RECIST

Response and progression evaluation will be performed according to Novartis RECIST guideline (as described in detail in section 16.2 of the Clinical Study Protocol), which is based on RECIST version 1.1 (Eisenhauer et al 2009). The text below gives instructions and rules to provide details needed for programming.

2.4.1 Best overall response (BOR)

The best overall tumor response will be assessed as per RECIST 1.1 criteria. The definitions and the details on the derivation are given in section 16.2 of the Clinical Study Protocol.

Only tumor assessments performed before the start of any anti-neoplastic therapies (i.e. any additional anti-neoplastic therapy or surgery) and within 30 days after the last administration of study treatment will be included in the assessment of best overall response.

- New anti-neoplastic therapies will be identified from the data collected on ‘Anti-neoplastic therapies since discontinuation of study treatment’ CRFs.
- Palliative radiotherapy is the only setting of radiotherapy allowed during the study. Therefore, palliative radiotherapy will not be considered as an anti-neoplastic therapy for assessment of BOR. As per RECIST 1.1, it should not be delivered to a target lesion.
- Continuation of combination partner therapy alone after end of study treatment will also not be considered as a new anti-neoplastic therapy.

The standard definition of a best overall response evaluation of ‘stable disease’, ‘disease progression’ or ‘unknown’ given in the section 16.2 of the Clinical Study Protocol will be used for this study. Best overall response for each patient is determined from the sequence of overall (lesion) responses (as reported by the investigator for local BOR, and as reported by BIRC for central BOR) according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.

- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment (or better) > 6 weeks after randomization (and not qualifying for CR or PR).
- Non-CR/non-PD = at least one non-CR/non-PD assessment (or better) > 6 weeks after randomization date (and not qualifying for CR). This applies only for patients with non-measurable disease alone at baseline. Non-CR/non-PD may only occur in the BIRC assessments given that measurable disease is one of the study inclusion criteria.
- PD = progression ≤ 12 weeks after randomization (and not qualifying for CR, PR, SD and non-CR/non-PD)
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD or non-CR/non-PD after more than 6 weeks or without progression within the first 12 weeks).

Patients with best overall response "unknown" will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early (≤6 weeks after randomization)
- PD too late (>12 weeks after randomization and not qualifying for CR, PR and SD)

Special (and rare) cases where BOR is unknown due to both early SD and late PD will be classified as "SD too early".

2.4.2 Disease progression

Progressive disease should only be assigned if it is confirmed by an assessment method as per RECIST 1.1 guidelines (e.g. radiologic assessment, photos for skin lesions, etc.). If a new lesion is detected using an objective assessment method other than radiologic assessment, then it should also be entered on the 'New lesion' RECIST CRF with appropriate method. Discontinuation due to disease progression or death due to study indication, without corresponding supportive data in the RECIST CRF (as defined above), will not be considered as progressive disease in the calculation of best overall response and in the analysis of PFS.

2.4.3 Change in imaging modality

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from 'with' to 'without' contrast use or vice-versa, regardless of the justification for the change), a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in an UNK (unknown) overall lesion response based on the Novartis calculation. However, a response from the investigator or the central blinded reviewer that differs from the Novartis calculated UNK is acceptable, if a definitive response assessment can be justified based on the available information.

Potential discrepancies between the modality used and overall lesion response (e.g. change in modality but response is different from 'Unknown') will be queried during the data validation process.

2.4.4 Determination of missing adequate assessments

The term 'missing adequate assessment' refers to assessments that are not done or for which the overall lesion response is 'Unknown'. 'Missing adequate assessment' will also be referred to as 'missing assessment'.

As detailed in Section 5.2.5 and in section 16.2 of the Clinical Study Protocol, the PFS censoring and event date options depend on the presence and the number of missing tumor assessments. An event occurring after two or more missing assessments is censored at the last adequate tumor assessment.

An exact rule to determine whether there are no, one or two missing TAs is therefore needed. This rule is based on the interval between the last adequate tumor assessment (LATA) date and the event date. The scheduled date of tumor assessments (in weeks from randomization), protocol specified window for tumor assessments, and the thresholds for LATA that belong to a visit can be found in the following table.

Table 2-2 Schedule for tumor assessment and time windows

Assessment schedule		Scheduled date – 1 week	Scheduled date (weeks from randomization)	Scheduled date +1 week	Threshold*
Every 8 weeks for the first 18 months	Baseline	0	0	0	0
	C3D1	7	8	9	12
	C5D1	15	16	17	20
	C7D1	23	24	25	28
	C9D1	31	32	33	36
	C11D1	39	40	41	44
	C13D1	47	48	49	52
	C15D1	55	56	57	**60**
	C17D1	63	64	65	**68**
	C19D1	71	72	73	78
Every 12 weeks after 18 months	C22D1	83	84	85	90
	C25D1	95	96	97	102
	C28D1	107	108	109	114
	C31D1	119	120	121	126
* The mid-point between current and next visit (except for baseline) and the upper limit for LATA to be matched to a certain scheduled assessment, e.g. if LATA is at week 13, this is after threshold for C3D1 and before that for C5D1, so the matching scheduled assessment is C5D1.					

To calculate the number of missing tumor assessments, the LATA before an event is matched with a scheduled tumor assessment using the time window in Table 2-2 (essentially whichever scheduled assessment it is closest to). Two thresholds, D1 and D2 are calculated for that scheduled assessment based on the protocol-specified schedule and windows

- An event after LATA+D1 will be considered as having >=1 missing assessment
- An event after LATA+D2 will be considered as having >=2 missing assessments

Since there is a change of schedule for tumor assessments at 18 months, D1 and D2 are defined differently depending on when LATA happens.

Rule 1: if LATA happens within 60 weeks from randomization (the matched scheduled tumor assessment is C15D1 or before)

- D1=8+2=10 weeks
- D2=2*8+2=18 weeks

Rule 2: if LATA happens after 60 weeks but within 68 weeks from randomization (the matched scheduled tumor assessment is C17D1)

- D1=8+2=10 weeks
- D2=8+12+2=22 weeks

Rule 3: if LATA happens after 68 weeks from randomization (the matched scheduled tumor assessment is C19D1 or later)

- D1=12+2=14 weeks
- D2=2*12+2=26 weeks.

Therefore, using the D2 definition above, the censoring of an event occurring after ≥2 missing TAs (in the primary PFS analysis) can be refined as follows: if the distance between the last adequate TA date and the PFS event date is larger than D2, then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

The same definition of D2 will be used to determine the PFS censoring reason. If the distance between the last adequate tumor assessment date and the earliest of the following dates (analysis cut off, consent withdrawal etc.) is less than or equal to D2:

1. Analysis cut-off date
2. Date of consent withdrawal
3. Start date of further anti-neoplastic therapy
4. Date of loss to follow-up

then the censoring reason will be 1. 'Ongoing without event', 2. 'Withdrew consent', 3 "New cancer therapy added" or 4. 'Lost to follow-up', respectively. However, if this distance is larger than D2, then the censoring reason will be 'Adequate assessment no longer available'. If an event is documented after two missing assessments, then the censoring reason will be 'Event documented after two or more missing tumor assessments'.

2.4.5 No baseline tumor assessments

Patients with no baseline tumor assessment will be excluded from the per protocol set.

For the PFS analysis, as specified in section 16.2 of the Clinical Study Protocol, since the timing of disease progression cannot be determined for patients with missing baseline tumor assessment, these patients are censored in the PFS analysis at the date of randomization. This rule however only applies to the disease progression component of the PFS assessment, and not to the survival component. Patients without baseline tumor assessments who die within D2

distance (see Section 2.4.4 for definition) of randomization will be counted as having an event in the PFS analysis at the date of death.

2.4.6 Construction of waterfall graphs

Waterfall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall graphs.

Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. As a conservative approach, such assessments will not be considered for display as bars in the graph, since the percentage change in the sum of diameters of target lesions reflects the non-PD target lesion response, but the overall lesion response is PD. A patient with only such assessments will be represented by a special symbol (e.g. ✶) in the waterfall graph.

Assessments with "unknown" target lesion response and assessments with unknown overall response will be excluded from the waterfall plots. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of patients with tumor shrinkage and tumor growth. A footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-3.

Table 2-3 Assessments considered for calculation of best percentage change for waterfall graphs

Case	Target response	Overall lesion response	Calculate % change from baseline in sum of diameters?
1	UNK	Any	No, exclude assessment
2	Any	UNK	No, exclude assessment
3	CR/PR/SD	PD	No, flag assessment with ✶
4	PD	PD	Yes
5	CR/PR/SD	CR/PR/SD	Yes

2.5 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics/prognostic data will be summarized descriptively by treatment group for the FAS. Relevant medical history and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group in the FAS. The summary will also be produced for the PPS if the FAS and PPS differ.

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

2.5.1 Patient disposition

Patient disposition for all randomized patients will be summarized. There will be one combined by-treatment summary showing:

1. Number (%) of patients treated/untreated
2. Number (%) of patients who are still on-treatment (based on the absence of the 'End of treatment' page)
3. Number (%) of patients who discontinued study treatment (based on the 'End of Treatment' page)
4. Reasons for study treatment discontinuation (based on 'End of Treatment' page)
5. Number (%) of patients who entered the post-treatment evaluations (based on 'End of Treatment' page)
6. Number (%) of patients who discontinued from the post-treatment evaluations (based on 'End of post treatment follow up disposition' page and 'Subject status' page)
7. Reasons for discontinuation from the post-treatment evaluations phase (based on 'End of post treatment follow up disposition' page and 'Subject status' page)

Enrollment by country and center will be summarized for all screened patients and the summary will also include number (%) of patients by treatment arm using the FAS.

In a separate summary, the reasons for patients not completing the screening phase will be presented based on the "Screening Phase Disposition" CRF.

2.5.2 Basic demographic and background data

Demographic and background disease characteristics data will be listed in detail. Qualitative data (e.g. race, ECOG performance status, etc.) will be summarized by means of contingency tables by treatment arm and quantitative data (e.g. age, body weight, etc.) will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum, and maximum) by treatment arm.

Discrepancies between randomization stratification information (obtained from the Interactive Response Technology (IRT) system) and stratum information based on data collected on CRFs will be tabulated and listed.

Unless otherwise specified, stratified analyses and analyses "by stratum" will be based on IRT stratification data, while data for other subgroup analyses will be based on CRF data.

2.5.3 Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, histological grade, stage at initial diagnosis, time since initial diagnosis, stage at time of study entry, presence/absence of target and non-target lesions, number and type of metastatic sites involved, HER-2 / estrogen / progesterone receptor status, disease-free interval (DFI) for non-de novo patients, and a categorization of prior (neo-) adjuvant endocrine therapy (ET) as outlined below:

- De novo patients will be identified as those with "De novo" box ticked in the eCRF.
- DFI for non-de novo patients will be calculated as the time from initial diagnosis to recurrence/progression and categorized as ≤12 months and >12 months.
- Patients will be grouped as follows based on prior (neo-)adjuvant ET:

- No prior (neo-)adjuvant endocrine therapy
- Progression while on or within 12 months of end of (neo-)adjuvant ET
- Progression > 12 months after end of (neo-)adjuvant ET.

Time since initial diagnosis will be summarized in months. A month is defined as 365.25/12=30.4375 days.

2.5.4 Medical history

Medical history and ongoing conditions, including cancer-related conditions, will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class and preferred term. Medical history/current medical conditions are coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of the analyses. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.5.5 Prior anti-neoplastic therapy

The number and percentage of patients recording any prior anti-neoplastic medications, radiotherapy or surgery (biopsy and non-biopsy separately) will be summarized by treatment arm both separately and in a combined fashion.

- Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy etc.), and also by lowest ATC class, preferred term and treatment. The total number of regimens along with the type (e.g. hormonal therapy), setting (e.g. adjuvant), and time from treatment end date of the last therapy to progression will be summarized by treatment arm.
  - Hormonal therapy (letrozole/anastrozole) for advanced breast cancer received for ≤ 14 days with or without goserelin, or treatment with goserelin for ≤ 28 days prior to randomization, as permitted by the study protocol, will be summarized separately.
  - Hormonal therapies in (neo-)adjuvant setting will also be summarized, including time from last dose of (neo-)adjuvant hormonal therapy to randomization.
- For radiotherapy, the setting (e.g. adjuvant, palliative) for the last therapy will be summarized.
- For surgery (excluding biopsies), the time since last surgery will be summarized by treatment arm.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

2.5.6 Other and COVID-19 Pandemic

All data collected at baseline, including patients' referrals, will be listed.

Recruitment in the study was ongoing during the onset of the COVID-19 pandemic. The baseline demographic characteristics, diagnosis and extent of cancer, and prior anti-neoplastic therapy will be summarized seperately for patients randomized before the COVID-19 pandemic start and patients randomized after the COVID-19 pandemic start.

The start date of the COVID-19 pandemic in each region/country is defined as the approximate time point at which, according to the WHO situation reports and the Johns Hopkins database, the number of confirmed COVID-19 infections started to increase significantly (around 100 confirmed cases) and / or governments started to take measures (such as lockdown and stay-at-home orders) to contain the spread of the infection, whichever occurred first. As of March 1, 2020, given the reach of the pandemic (as documented by WHO situation report 40) and media coverage around the world at that point in time, it is assumed that most locations could have been affected by actions related to COVID-19 (e.g. restrictions of mobility at regional or local level, measures taken by clinical sites, etc.) The detailed start dates are listed in Table 2-4.

Table 2-4 COVID-19 start date

Region/Country	Start Date
China	01-Jan-2020
South Korea	20-Feb-2020
Japan	21-Feb-2020
Italy	23-Feb-2020
Rest of the World	01-Mar-2020

Considering that no patients were enrolled in China, South Korea, Japan and Italy in this study, the start date of COVID-19 is defined as 01-Mar-2020.

2.6 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.6.1 Study treatment / compliance

Duration of study treatment exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment. The number of patients with dose reductions/interruptions and the reasons, will be summarized and listed. Details of the derivations and summaries are provided in the following sections.

The safety set will be used for all summaries and listings of study treatment.

2.6.1.1 Duration of study treatment exposure

The duration of exposure to study treatment will be calculated as:

Duration of exposure to study treatment (days) = (***last date of exposure*** to any study treatment component) – (date of first administration of study treatment) + 1.

Duration of exposure to any single component of study treatment will be calculated as:

Duration of exposure (days) = (last date of exposure to study treatment component) – (date of first administration of study treatment component) + 1.

The ***last date of exposure*** is defined as follows for the study treatment components:

- For ribociclib, anastrozole, and letrozole: the last date of exposure is defined as the date of last administration of the corresponding medication;
- For goserelin, the last date of exposure is defined as the date of last administration of goserelin + 27 days.

- If a patient died or was lost to follow-up within date of last administration + 27 days, then the last date of exposure is the date of death or the date of lost to follow-up as recorded in the disposition panel, respectively.

This duration of exposure includes the periods of temporary interruption (of any component of the study treatment for any reason). The duration of study treatment exposure and exposure to each treatment component will be summarized by treatment arm. In addition, the duration of exposure will be categorized into time intervals (e.g. <3 months; 3-<6 months; 6-<9 months, etc.); frequency counts and percentages will be presented for the number of patients in each interval.

2.6.1.2 Cumulative dose and average daily dose

Cumulative dose for any component of study treatment is defined as the total dose of the medication given during the study treatment exposure.

Average daily dose is defined as [Cumulative dose (mg) / Number of dosing days]; drug free day(s) are not counted as dosing days.

Cumulative dose and average daily dose will be summarized using descriptive statistics by treatment arm for each component of study treatment. Patients with no exposure to the study treatment component will be excluded from the corresponding summary.

2.6.1.3 Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure to each study treatment component is defined as follows:

For letrozole, and anastrozole, DI is defined as

DI (mg/day) = Cumulative dose (mg) / duration of exposure to study treatment component (days).

For goserelin, DI is defined as

DI (mg/28 days) = Cumulative dose (mg) / {[(date of last administration of goserelin + 27) – (date of first administration of goserelin) + 1] / 28},

to account for the goserelin dosing schedule in the DI computation.

For ribociclib, DI is defined as

DI (mg/day) = Cumulative dose (mg) / *adjusted* duration of exposure to ribociclib (days),

where *adjusted* duration of exposure (days) to ribociclib represents the number of ribociclib dosing days a patient would be expected to have received per protocol, given their duration of exposure to ribociclib as defined in Section 2.6.1.1. Since ribociclib follows a 3 weeks on, 1 week off schedule, the adjusted duration of exposure to ribociclib is the duration of exposure to ribociclib minus the planned off days. The adjusted duration of exposure to ribociclib is therefore 21 x (# completed 28 day cycles) + min (21, duration of last incomplete cycle).

For example, if the duration of exposure to ribociclib is 66 (corresponding to two cycles and 10 days), then the adjusted duration of exposure to ribociclib is 21*2+10=52. If the duration of exposure to ribociclib is 108 days (corresponding to three cycles and 24 days), then the adjusted duration of exposure is 21*3+21=84 days.

Specifically, let D1 represent the duration of exposure to ribociclib as defined in Section 2.6.1.1. Then the adjusted duration of exposure is defined as

D=21*[D1/28]+min(21,D1-28*[D1/28]) days,

where [x] stands for the integer part of x. In this equation [D1/28] is the number of completed cycles, and D1-28*[D1/28] is the additional number of days in the last, incomplete cycle (if any). For example, if D1=30 then [D1/28]=1, D1-28*[D1/28]=2, and D=23. If D1=7 then D=7; if D1=22 then D=21; if D1=28 then D=21, etc.

Planned dose intensity (PDI) is defined as the assigned dose by unit of time planned to be given to patients as per protocol. The PDI for each study treatment component is displayed in Table 2-5. Note that DI will also be calculated and reported in the units displayed in Table 2-5, whereas duration of exposure itself will be summarized in months.

Table 2-5 Planned dose intensity

Medication	PDI (dose unit/unit of time)
Ribociclib	400 mg/day for the experimental arm 600 mg/day for the control arm
Letrozole	2.5 mg/day
Anastrozole	1 mg/day
Goserelin	3.6 mg/28 days

Relative dose intensity (RDI) is defined as:

RDI = DI (dosing unit / unit of time) / PDI (dosing unit / unit of time).

DI and RDI will be summarized separately for each of the study treatment components.

2.6.1.4 Dose reductions, interruptions and delays

The number and percentage of patients with dose reductions, interruptions or delays, and the reasons, will be summarized by treatment arm as outlined below.

Interruption: An interruption is defined as a 0 mg dose given on one or more days during the period where (for ribociclib only) a patient is not on the "off" part of a treatment cycle, after which > 0mg dose resumes. For patients who had dose interruption checked but never resumed non-zero dose, the dose interruption will not be counted. For example, in the sequence of 600 mg – 0mg (dose break) -0mg (dose interruption) – 0 mg (dose permanently discontinued) the 0mg (dose interruption) will not be counted as a dose interruption. Interruptions will be summarized for each component of study treatment.

Delay: A special case of an interruption is one that, for ribociclib, occurs at the start of a new cycle, after a planned rest period. Such instances will be identified as a subset of the interruptions (specifically those occurring directly after a planned dose break) and will be summarized separately as dose delays.

Reduction: A dose reduction for ribociclib is defined as a decrease from the previous non-zero dose to another non-zero dose less than the protocol-planned dose, even if this decrease has been directly preceded by an interruption. For example, in the sequence 600 mg – 0mg – 400 mg, the 400mg dose will be counted as a reduction.

If due to dosing error, a patient took a dose during the dosing break with a dose that is lower than the previous dose but resumed the correct dose subsequently, this will not be considered as a dose reduction. For example, a patient took 600 mg from day 1-5, then mistakenly took 200 mg per day on day 6-8, then resumed 600 mg dosing on day 9. This will not be considered as a dose reduction.

As a sensitivity analysis for short duration of dose reduction arising from dosing error, summary of dose reduction will also be produced excluding the dose reduction episodes due to dosing error lasting less than 28 days.

Missing data: If dose is recorded but frequency is missing or entered as 'none', it is assumed that the study drug was taken as per-protocol.

In this study, dose reductions for letrozole, anastrozole or goserelin are not permitted and will not be summarized, however all dosing data will be listed.

2.6.1.5 Discontinuation of study treatment components

The reasons for discontinuation of each study treatment component will be summarized by treatment arm, based on the information on the component-specific end of treatment CRFs.

2.6.2 Concomitant therapy and post treatment anti-cancer therapies

Concomitant therapy

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that were administered to a patient, coinciding with the study assessment period (even if started before the study assessment period).

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system.

Concomitant medications will be summarized by lowest ATC class, preferred term and treatment arm. These summaries will include:

1. medications starting on or after the start of study treatment but no later than 30 days after last dose of study treatment, and
2. medications starting prior to the start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

The safety set will be used for all concomitant medication tables and listings.

Concomitant medications that have the potential to impact some specific analyses (e.g. PK, efficacy or safety analyses) will be identified prior to database lock. Separate summaries of these concomitant medications will be produced using the appropriate analysis set (e.g. FAS for those potentially affecting efficacy).

- Strong inhibitors or inducers of CYP3A4/5, substrates of CYP3A4/5 with a narrow therapeutic window, medications with a known risk of QT prolongation and other

prohibited medications described in Section 2.3 will be identified. They will be tabulated by ATC class and preferred term.

- Any anti-neoplastic therapies administered concomitantly with study treatment will be listed based on their identification through the protocol deviation process.

Post treatment anti-cancer therapy

Anti-neoplastic therapies after discontinuation of study drug will be listed and tabulated by ATC class, preferred term and treatment arm by means of frequency counts and percentages using the FAS.

2.7 Analysis of the primary objective

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

2.7.1 Primary endpoint

The primary endpoint of the study is overall response rate (ORR), defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) assessed by local investigators according to RECIST 1.1 (See protocol Section 16.2 for further details for RECIST 1.1). ORR is based on the tumor evaluations from patients who have been treated for at least 6 months or have discontinued treatment. The cut-off date for the primary analysis will be established based on the description in Section 2.1. The primary efficacy variable, ORR, will be based on the PPS population according to the randomized treatment group.

The tumor endpoint derivation is based on the sequence of overall lesion responses at each assessment/time point. However, the overall lesion response at a given assessment/time point may be provided from different sources as illustrated in Table 2-6.

Table 2-6 Sources for overall lesion response

Source 1	Investigator (local radiology) reported overall lesion response
Source 2	Novartis-calculated overall lesion response based on raw (i.e. individual lesion) measurements from investigator (local radiology)
Source 3	Final BIRC-reported overall lesion response

The primary efficacy analysis will be based on the investigator/local radiology review. The investigator reported overall lesion response at each assessment/time point (Source 1 in Table 2-6) will be used to derive the efficacy endpoints.

The overall response at each assessment will also be calculated using the raw lesion measurements (Source 2 in Table 2-6). The calculated responses will be listed along with the responses given by the investigator. As a sensitivity analysis, ORR based on calculated overall lesion response (Source 2 in Table 2-6) will also be summarized.

Tumor assessment data based on BIRC assessment (Source 3) will be used for selected supportive efficacy analyses. The BIRC consists of two independent radiologists and an adjudicator. The BIRC-reported overall lesion response data will be used to derive the BIRC-based endpoints. Data from independent readers will be listed together with the adjudication. Differences in overall responses between local radiology (Source 1) and central radiology (Source 3) will be listed.

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 Hypothesis and test statistic

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

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

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

The CI of ORR ratio will be constructed using Mantel-Haenszel method to include lung/liver metastasis as the stratification factor (strata based on IRT data).

2.7.2.2 ORR and Wald confidence intervals

ORR will be presented by treatment arm along with standard Wald asymptotic (i.e. normal approximation) 95% confidence intervals.

2.7.3 Handling of missing values/censoring/discontinuations

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

2.7.4 Sensitivity and Supportive analyses

Sensitivity analyses

As a sensitivity analysis to assess the impact of stratification, the primary endpoint will be repeated in an unstratified test in the PPS.

As a sensitivity analysis, the primary analysis for ORR with and without stratification will also be repeated in the FAS.

Supportive analyses

As a supportive analysis, the primary analysis will be repeated using Blinded Independent Review Committee (BIRC) assessment and Novartis calculated overall lesion response in both the PPS and FAS.

Subgroup analyses to assess the homogeneity of overall response rate based on demographic and baseline disease characteristics will be performed in both arms; the subgroups to be included is defined in Section 2.2.5. The analysis will be conducted in both the PPS and FAS.

2.8 Analysis of the key secondary objective

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

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

QTcF collected at all the timepoints including Cycle 1 Day 15 (2h post-dose) will also be summarized by treatment arm as one of secondary objectives as specified in Section 2.10.4.

2.9 Analysis of secondary efficacy objective(s)

2.9.1 Progression free survival (PFS)

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

PFS will be analyzed in the FAS population according to the randomized treatment group as follows:

- The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.
- Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by treatment arm based on the reasons defined in Section 2.4.4. These summaries on censoring reasons will be produced for PFS by investigator radiology and BIRC review.
- Comparison of PFS event type/censor between local radiology review and BIRC review

No inferential analysis that compares progression free survival between the two treatment arms will be performed.

2.9.2 Clinical benefit rate (CBR)

CBR is defined as the proportion of patients with a best overall response of complete response (CR), or partial response (PR), or an overall response of stable disease (SD), lasting for at least 24 weeks. CR, PR, and SD are defined as per local review as well as BIRC according to RECIST 1.1 (see protocol Section 16.2 for further details). A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 24-1=23 weeks or later from randomization, allowing for the ±1 week visit window for tumor assessments. For BIRC assessment, NCR-NPD might be recorded if the BIRC reviewer is not able to identify target lesion at the baseline, and in this case, NCR-NPD will be handled in the same way as SD in terms of CBR calculation.

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

No inferential analysis that compares CBR between the two treatment arms will be performed.

2.9.3 Time to response (TTR)

TTR is defined as the time from the date of randomization to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (although date of initial response is used, not date of confirmation). CR and PR are based on tumor response data as per local review and according to RECIST 1.1 (see protocol Section 16.2 for further details).

All patients in the FAS will be included in TTR calculations. Patients without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e. LPLV-FPFV) for patients with a PFS event (i.e. disease progression or death due to any cause), or at the date of the last adequate tumor assessment for patients without a PFS event.

TTR will be listed and summarized by treatment arms. The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. A descriptive summary of time to response for the responders will also be presented.

No inferential analysis that compares TTR between the two treatment arms will be performed.

2.9.4 Duration of response (DOR)

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

DOR will be listed and summarized by treatment group for all patients in the FAS with confirmed BOR of CR or PR (see protocol Section 16.2 for further details). The distribution of duration of response will be estimated using the Kaplan-Meier method and the median response duration will be presented along with 95% confidence interval only if a sufficient number of responses is observed.

No inferential analysis that compares DOR between the two treatment arms will be performed.

2.9.5 ECOG performance status

The ECOG PS scale (Table 2-7) will be used to assess physical health of patients, ranging from 0 (most active) to 5 (least active):

Table 2-7 ECOG Performance Scale

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

The following intervals will be used to group the ECOG PS data over time. Day in columns 2 and 3 is defined as date of ECOG PS assessment date – randomization date + 1. The correspondence with Day in column 1 assumes that a patient is treated on the day of randomization; however the definition of Day in columns 2 and 3 still applies if this is not the case, i.e. randomization date is taken as the reference for the windows.

Table 2-8 Time windows for ECOG PS assessments

Assessment	Target day of assessment	Time Interval
Baseline		Day 1 (if not available use screening)
Cycle 1 Day 15	15	Day 2 to day 21
Cycle 2 Day 1	29	Day 22 to day 42
Cycle 3 Day 1	57	Day 43 to day 63
Cycle 3 Day 15	71	Day 64 to day 77
Cycle 4 Day 1	85	Day 78 to day 98
Cycle k Day 1 (k≥7)	d=(k-1)*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the worst of the 2 assessments will be used.

Frequency counts and percentages of patients in each score category will be provided by treatment arm and time point.

2.10 Safety analyses

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for deaths, including on-treatment and post treatment deaths will be provided.

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

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

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

2.10.1 Adverse events (AEs)

2.10.1.1 General rules for AE Reporting

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

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

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

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

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

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment. A patient with multiple grades for an AE will be summarized under the maximum grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the ribociclib arm.

The frequency of grade 3 and above AEs will be summarized separately.

Any information collected (e.g. grades, relationship to study treatment, serious, action taken etc.) will be summarized as appropriate.

All AEs, deaths, and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

2.10.1.2 AE and deaths summaries

The following adverse event summaries will be produced:

- Summary of deaths and adverse events
- AEs, irrespective of causality, by primary system organ class, preferred term and maximum grade
- AEs with suspected relationship to study treatment by primary system organ class, preferred term and maximum grade
- Most common grade ≥3 adverse events, irrespective of causality, by preferred term and maximum grade (greater than x% in either arm)
- Adverse events, irrespective of causality, by primary system organ class and maximum grade
- Adverse events, irrespective of causality, by preferred term and maximum grade
- Adverse events with suspected relationship to study treatment by preferred term and maximum grade
- Grade 3 and above AEs, irrespective of causality, by primary system organ class, preferred term and maximum grade
- Grade 3 and above AEs with suspected study treatment relationship by primary system organ class, preferred term and maximum grade
- On-treatment deaths, by preferred term
- All Deaths (on-treatment + post-treatment), by primary system organ class and preferred term
- Serious AEs, irrespective of causality, by primary system organ class, preferred term and maximum grade
- Serious AEs with suspected relationship to study treatment, by primary system organ class, preferred term and maximum grade
- AEs leading to discontinuation, irrespective of causality, by primary system organ class, preferred term and maximum grade
- AEs requiring dose adjustment , irrespective of causality, by primary system organ class, preferred term and maximum grade
- AEs requiring treatment interruption, irrespective of causality, by primary system organ class, preferred term and maximum grade

- AEs requiring additional therapy, irrespective of causality, by primary system organ class, preferred term and maximum grade
- Non-serious AEs (at least x% incidence rate in either treatment arm) by primary system organ class and preferred term.
- Serious and non-serious adverse events with number of occurrences (an occurrence is defined as >1 day between start and prior end date of record of same preferred term)
- On-treatment deaths and SAEs with fatal outcome, by SOC and PT

2.10.1.3 Grouping of AEs of special interest (AESI)

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to ribociclib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLTs (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, the number and percentage of patients with at least one event of the AESI occurring during the on-treatment period will be summarized.

Summaries of these AESIs will be provided by treatment arm (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, etc.).

A Case Retrieval Sheet (CRS) with the exact composition of the AE groupings is to be used to map reported AEs to the AESI groupings. This file may be updated (i.e. it is a living document) based on review of accumulating trial data, and therefore the groupings are also subject to potential change. Table 2-9 provides the latest groupings at the time of the finalization of the SAP. The most up-to-date version of the CRS will be used at the time of the analysis.

Table 2-9 AESI groupings

AESI grouping	MedDRA category
Anemia	SMQ
Diarrhea	SMQ
Hepatobiliary toxicity	SMQ
Infections	SMQ and SOC
Leukopenia	HLT
Nausea, emesis	HLT
Neutropenia	HLT and PT
Pneumonitis, interstitial lung disease	SMQ
Pulmonary embolism	SMQ and HLT
QTc prolongation	SMQ
Renal impairment	SMQ
Reproductive toxicity	SMQ
Thrombocytopenia	SMQ

2.10.2 Laboratory data

On analyzing laboratory data, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected no later than 30 days after the last administration of study treatment. All laboratory assessments will be listed and those collected later than 30 days after the last treatment date will be flagged in the listings

All laboratory data will be listed by treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. The criteria to assign CTC grades are given in Appendix 1.

The following summaries will be produced for the laboratory data (by laboratory parameter):

- Number and percentage of patients with each CTC grade as their worst post-baseline value (regardless of the baseline status). Each patient will be counted only for the worst grade observed post baseline.
- Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.
- Number and percentage of patients meeting categorical liver function test criteria, including ALT, AST and ALT/AST (>3x, 5x, 8x, 10x, 20x ULN), Total Bilirubin (>1x, 2x ULN), ALP (>1.5x, 2x, 3x, 5x, 8x, 10x ULN), combined categories of ALT/AST and total bilirubin (e.g., ALT/AST>3x ULN & total bilirubin > ULN) as well as potential Hy's Law criteria (ALT or AST > 3 x ULN and TBIL > 2 x ULN and ALP < 2 x ULN). For the combined categories, the assessments need not be concurrent, i.e. patients are counted based on their most extreme value for each parameter (highest in the case of ALT, AST and TBIL; lowest in the case of ALP).
- Box plots of laboratory values by scheduled time point and treatment arm.

The following listings will be produced for the laboratory data:

- Listing of patients with CTC grade 3 or 4 laboratory abnormalities;
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

Time to first occurrence of grade 2 or worse laboratory toxicity and time to first occurrence of grade 3 or worse laboratory toxicity will be performed for (i) neutropenia and (ii) ALT/AST. Median time to first occurrence and 95% CI will be provided based on the Kaplan-Meier method. In addition, Kaplan-Meier plots will be generated.

Time to first occurrence of grade X or worse laboratory toxicity is defined as the time from the start of treatment to the start date of the first incidence of grade X or worse laboratory toxicity,

i.e. time in days is calculated as (start date of first occurrence) – (date of first dose of study treatment) +1. A patient will be censored if:

- The patient did not report any post-baseline grade X or worse event on or before the analysis cut-off date.
- The patient discontinued treatment without reporting any grade X or worse event up to 30 days after study treatment discontinuation.
- The patient died without reporting any grade X or worse event.
- The patient received a new anticancer therapy before reporting any grade X or worse event.

The censoring date will be the earliest of the following dates: end of treatment + 30 days, analysis cut-off, new anti-cancer therapy start date, death date and last non-missing assessment for the lab parameter. Note that patients who have grade X or worse toxicity at baseline or missing baseline evaluation will be excluded from this analysis.

In addition, the median time to first occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

Duration of grade X or worse laboratory toxicity may also be summarized. Duration of grade X or worse event is calculated as:

(Date when the grade of the event decreases to below X) – (date of onset of grade X or worse event) + 1

For patients experiencing any grade X or worse event, the duration of the first such event will be summarized using the Kaplan-Meier method. Median duration and 95% CI will be presented. In addition, Kaplan-Meier plots will be generated.

A patient will be censored for the duration of grade X or worse event, if:

- The patient dies without reporting a decrease to below grade X
- The patient receives a new anticancer therapy before reporting a decrease to below grade X
- The patient discontinues from the study treatment without reporting a decrease to below grade X up to 30 days after study treatment discontinuation
- The patient is still ongoing at the analysis cut-off date without reporting a decrease to below grade X

The censoring date is the earliest of the following dates: end of treatment + 30 days, analysis cut-off, new anti-cancer therapy start date, death date and last non-missing assessment for the lab parameter.

2.10.3 ECG and cardiac imaging data

All analyses of ECG data will be based on the average of all available replicate ECGs assessed at each time point for each patient. For unscheduled assessments, 15-minute windows will be applied to group assessments for averaging.

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

Change from baseline of QTcF at time points including Cycle 1 Day 15 as specified in Section 2.8 will also be summarized. Notable elevations of QTcF will be summarized based on all on-treatment ECG assessments. The totality of the safety data obtained in Arms 1 and 2, generated from each time point as outlined in the ECG monitoring and assessment schedule including PR, QRS, QT, and RR intervals, will be compared as part of the overall assessment for QT prolongation risk mitigation.

Notable elevations of ECG summarize the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc interval data/PR/RR/QRS or changes from baseline as defined in Table 2-10, and notable elevations of ECG summary includes only newly occurring ECG abnormality. A newly occurring ECG abnormality is defined as an abnormal post-baseline ECG finding that is not present at baseline. The percentage of patients having notable ECG interval values is based on the number of patients at risk for the change with a value at baseline and post-baseline.

Table 2-10 Clinically notable ECG values

ECG parameter (unit)	Clinically notable criteria
QT, QTcF, QTcB (ms)	New > 450 New > 480 New > 500 Increase from Baseline > 30 Increase from Baseline > 60
PR duration (ms)	Increase > 25% from baseline and to PR duration > 200 New > 200
QRS duration (ms)	Increase > 25% from baseline and to QRS duration > 110 New > 110
Heart Rate (bpm)	< 50 and decrease from Baseline of > 25% > 100 and increase from Baseline of > 25%

Time to grade 2 or worse QT prolongation will be analyzed using the Kaplan-Meier method and the median time to grade 2 or worse QT prolongation will be presented along with a 95% confidence interval if there are sufficient numbers of events for each treatment group.

In addition, the median time to event for the subset of patients who experienced grade 2 or worse QT prolongation will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

Note that patients who have grade 2 or worse toxicity at baseline or missing baseline evaluation will be excluded from these analyses.

Further analysis includes shift table summarizing the baseline to worst on-treatment result of QT/QTc, and table with descriptive statistics at baseline, post-baseline time points and change from baseline to post-baseline time points.

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

2.10.4 Vital signs

Vital signs assessments are performed in order to characterize basic body function. The parameters expected to be collected include: height, weight, body temperature, pulse rate, and systolic and diastolic blood pressure.

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
- Body temperature: ≥ 39.1°C
- Pulse rate: ≥ 120 bpm with increase from baseline of ≥15 bpm

Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Body temperature: ≤ 35°C
- Pulse rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm

The following summaries will be produced for each vital sign parameter:

- Summary statistic for change from baseline to the worst post-baseline value (in both directions, i.e. from baseline to highest post baseline and from baseline to lowest post baseline value).
- Number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e. both elevated and below normal values).

In addition, the following two listings will be produced by treatment arm:

- Patients with clinically notable vital sign abnormalities.
- All vital sign assessments will be listed by patient and vital sign parameter.

In both listings, the clinically notable values will be flagged and also assessments collected later than 30 days after the last treatment date will be flagged.

2.10.5 Other safety data

Data from other tests will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

All assessments collected later than 30 days after the last treatment date will be flagged in the listings.

Any statistical tests performed to explore the data will be used only to identify any interesting comparisons that may warrant further consideration.

Subgroup analyses will be explored as described in Section 2.2.5.

2.11 Pharmacokinetic endpoints

2.11.1 General principle

All PK analyses will be based on the PAS, unless otherwise specified. Evaluability criteria described below for concentrations and parameters is based on the dose of the respective drug for which the PK corresponds to.

Evaluable concentrations are defined as those for which all of the following apply:

- samples taken within the following time windows around the scheduled time points:
  - Pre-dose: prior to dosing on the assessment day and collected at 24 ± 2 hours after the last dose
  - 2 h post-dose: within ± 15 minutes of the scheduled time point
  - 4 or 6 h post-dose: within ± 30 minutes of the scheduled time point
  - 24 h post-dose: within ± 2 hours of the scheduled time point
- no vomiting occurs within the first 4 hours of the last dose (pre-dose samples)
- no vomiting occurs within the first 4 hours of the current dose (post-dose samples)
- the concentration has not been flagged for exclusion by the pharmacokineticist
- for ribociclib concentrations, assessments with at least 10 consecutive days of ribociclib dosing (10 doses at 600 mg or 10 doses at 400 mg or 10 doses at 200 mg) immediately prior to the PK collection

A PK parameter will be considered as NOT evaluable if any of the following conditions are satisfied:

- vomiting occurs within 4 hours of the current or last dose
- for ribociclib, the patient did not receive at least 10 consecutive days of ribociclib dosing (10 doses at 600 mg or 10 doses at 400 mg or 10 doses at 200 mg) prior to and on the PK collection day
- the parameter is flagged for exclusion by the pharmacokineticist

For ribociclib concentrations, as well as for ribociclib PK parameters, patients will be classified into the following dose groups at C1D15 and timepoint:

- RIBO600: consists of all patients who provided evaluable concentrations/parameters after receiving at least 10 consecutive daily ribociclib doses of 600 mg immediately prior to the PK collection (for concentrations) or prior to and on the PK collection day (for parameters) without a dose change or interruption.
- RIBO400 consists of all patients who provided evaluable concentrations/parameters after receiving at least 10 consecutive daily ribociclib doses of 400 mg immediately prior to the PK collection (for concentrations) or prior to and on the PK collection day (for parameters) without a dose change or interruption.
- RIBO200 consists of all patients who provided evaluable concentrations/parameters after receiving at least 10 consecutive daily ribociclib doses of 200 mg immediately prior to the PK collection (for concentrations) or prior to and on the PK collection day (for parameters) without a dose change or interruption (if any).

At least ten consecutive doses are expected to provide adequate time to reach steady state for ribociclib at 600 mg, 400 mg or 200 mg.

Only evaluable PK concentrations/parameters which are not flagged for exclusion will be used for figures, summaries, and statistical analysis. Concentration and parameter listings will include all values, with flags indicating those excluded from analyses.

Ribociclib concentration and parameter summaries, figures, and listings will be presented by treatment arm.

PK data collected from this study may be combined with data from other studies to support a population PK analysis of ribociclib using non-linear mixed effect modeling; details will be provided in a separate analysis plan.

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

2.11.2 PK concentrations

Ribociclib plasma concentration data will be listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point.

Descriptive statistics of concentrations will include n, m (number of non-zero concentrations), mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum. Coefficient of variation CV (%) is calculated as follows: 100*(SD/arithmetic mean).

Geometric CV (%) is calculated as follows from non-zero values:

$$\mathrm{CV}(\%) = 100 \cdot \sqrt{\exp\left(\hat{\sigma}^2\right) - 1}$$

where $\hat{\sigma}^2$ denotes the variance of the log-transformed values.

Geometric mean and arithmetic mean (SD) concentration-time profiles on C1D15, as well as individual concentration-time profiles with median on C1D15 of ribociclib by treatment arm will be graphically presented.

2.11.3 PK parameters

In approximately 20 patients per arm, extensive PK sampling for ribociclib will be performed as detailed in Section 8.5.1 of study protocol. For these patients, PK parameters (if available) of ribociclib, including but not limited to those listed in Table 2-11, will be calculated from the individual concentration-time profile.

Pharmacokinetic parameters will be listed by treatment and patient. Descriptive summary statistics will include n, mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where n, median, minimum, and maximum will be presented.

Table 2-11 Noncompartmental pharmacokinetic parameters

AUC0-24	The AUC from time zero to 24 hours (ng*h/mL)
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (ng*h/mL)
AUCinf	The AUC from time zero to infinity (ng*h/mL)

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

2.11.1 Handling missing and invalid values

Plasma samples will be assayed for LEE011 concentrations by Novartis or Novartis designated laboratory using validated LC-MS/MS methods with a LLOQ of approximately 1.00 ng/mL for ribociclib.

All concentrations below the LLOQ will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV.

Any missing PK parameter data will not to be imputed.

2.12 PD and PK/PD analyses

Not applicable.

2.13 Patient-reported outcomes

Not applicable.

2.14 Biomarkers

Not applicable.

2.15 Other Exploratory analyses

Not applicable.

2.16 Interim analysis

No formal interim analysis is planned for this study. The primary analysis will be performed after all patients have been treated for at least 6 months or have discontinued study treatment. A final analysis will be performed after efficacy follow up is complete.

In order to minimize the potential impact of treatment knowledge, until the primary analysis is conducted, no aggregate statistical analyses shall be performed by treatment.

3 Sample size calculation

3.1.1 Primary endpoint(s)

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

Table 3-1 Primary endpoint: Overall Response rate (ORR)

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

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

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

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

In both studies, the patient population is similar to the one proposed for this study, as all patients have HR-positive, HER2-negative advanced breast cancer with no prior hormonal treatment for advanced disease; and the ORRs are also very similar in CLEE011A2301 and CLEE011E2301 despite the difference in the menopausal status of the study populations. The ORR up to 6-months was estimated to be 43.9% in ribociclib in combination with NSAI and 29.1% in NSAI alone by pooling patients with measurable disease from studies CLEE011A2301 and CLEE011E2301. As such, the NI margin is calculated based on 50% retention on the log-scale of the ratio of 43.9% to 29.1%, which leads to the NI margin of 0.814 (FDA 2016).

3.1.2 Secondary endpoint(s)

The key secondary endpoint of the study is to evaluate if the upper 90% confidence interval for the QTcF change from baseline at Cycle 1 Day 15 (2h post-dose) is less than 20 ms for the

experimental dosing arm (Arm 1). Assuming that the ΔQTcF standard deviation is 20 ms, the probability of meeting this threshold under different scenarios of ΔQTcF at the Cmax is presented in Table 3-2.

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

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

3.1.3 Sample size considerations for PK analysis

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

4 Change to protocol specified analyses

The protocol deviation, “Patient had dose reduction of ribociclib within cycle 1” is not considered as a protocol deviation in the analysis. Instead, it is just considered as a condition to exclude the patient from per protocol set in the analysis.

This protocol deviation was defined before the primary analysis to acturately capture the number of patients who had dose reduction within cyle 1. However, after further review, it is not a protocol deviaition from clinical perspective. So, it is excluded from protocol deviation summary tables and listings.

5 Details of statistical analysis

5.1 Baseline comparability

Appropriate descriptive summary statistics of baseline variables (see Section 2.5) will be provided as in-text tables in the core CSR and also in Section 14 in the post-text tables. The summaries will be grouped by treatment arms, but no p-values will be provided.

5.2 Mantel-Haenszel estimator for the ratio of ORR

Suppose patients in experimental arm ($i = 1$) and control arm ($i = 0$) are randomized with strata liver/lung metastasis ($j = 1,2$), and let x_{ji} and n_{ji} denote the number of responsers (i.e. CR, PR) and the number of patients in arm i and stratum j, respectively. Further, let x_j and n_j denote the number of responsers (i.e. CR, PR) and the number of patients in stratum j in both arms, respectively.

Confidence intervals for the ratio of ORR in the experimental arm to the control arm referred as common relative risk is calculated using the Mentel-Haenszel estimate of the common relative risk over strata (Mantel and Haenszel 1959, Agresti 2002):

$$\hat{\delta} = \frac{\Sigma_j^2 x_{j1} n_{j2}/n_j}{\Sigma_j^2 x_{j2} n_{j1}/n_j}$$

The confidence limits for the common relative risk is then calculated using normal approximation after log transformation for $\hat{\delta}$. Therefore, the $100(1-\alpha)\%$ confidence interval for $\log(\hat{\delta})$ is given by

$$\log(\hat{\delta}) \pm z_{\alpha/2}\hat{\sigma}$$

where $z_{\alpha/2}$ is $1-\alpha$ percentile of standard normal distribution and $\hat{\sigma}$ is given by Greenland and Robins (1985):

$$\hat{\sigma}^2 = \widehat{var}\left(\log\left(\hat{\delta}\right)\right) = \frac{\Sigma_j^2 (n_{j1} n_{j2} x_j - x_{j1} x_{j2} n_j)/n_j^2}{(\Sigma_j^2 x_{j1} n_{j2}/n_j)(\Sigma_j^2 x_{j2} x_{j1}/n_j)}$$

The lower bound of the aforementioned confidence limit is $\hat{\delta}\exp\left(-z_{\alpha/2}\hat{\sigma}\right) = \exp(\log\left(\hat{\delta}\right) - z_{\alpha/2}\hat{\sigma})$ after exponentiation with $\alpha = 10$, which then will be compared with the pre-specified non-inferiority margin 0.814 as the primary analysis.

The Mantel and Haenszel approach for the calculation of confidence interval of relative risk is implemented in PROC FREQ with CMH option in the TABLE statement. Specifically, the TABLE statement is in the following order TABLE STRATA*TREATMENT*RESPONDER with option CMH1, and this will provide the point estimate as well as the confidence interval for$\hat{\delta}$.

5.3 Time-to-event analyses

The following sections present a general methodology to be used to analyze time-to-event variables, e.g.:

- Progression-free survival
- Time to response: defined as the time between date of randomization until first documented response (CR or PR) according to RECIST 1.1
- Duration of response
- Time to first occurrence of grade X or worse laboratory toxicity
- Time to grade 2 or worse QT prolongation

5.3.1 Analysis of time-to-event data with ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

5.3.2 Kaplan-Meier estimates

The survival function in each treatment arm will be estimated using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. Median survival for each treatment arm will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

5.3.3 The event/censor date for PFS analysis

The analysis of PFS will be based on the local radiological assessments (Source 1 in Table 2-6) as well as BIRC (Source 3 in Table 2-6). The analysis will be performed on the FAS and will use the default censoring and event date options from Table 16-8 of study protocol section 16.2 i.e. event/censoring rules will be based on options A(1), B(1), C1(1), C2(1), D(1), E(1), and F(2) (summarized in Table 5-1). In particular, PFS will be censored at the last adequate tumor assessment if a patient didn't have an event or the event occurred after two or more missing tumor assessments (see Section 2.4.4). PFS will also be censored at the last adequate tumor assessment prior to the start of a new antineoplastic therapy; i.e. option F(2) in Table 16-8 of protocol section 16.2 will be used.

Table 5-1 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization*	Censored
Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessments	Censored
No progression (or death)	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Date of last adequate assessment prior to new anticancer therapy	Censored
Treatment discontinuation due to 'Disease progression' without	Ignore clinical progression and follow situations above	As per above situations

documented progression, i.e. clinical progression based on investigator claim		
* The rare exception to this is if the patient dies no more than D2 days (see Section 2.4.4 for definition) after randomization, in which case this is a PFS event at the date of death		

5.4 Duration of follow-up

Study follow-up will be summarized using the following methods:

- Summary of duration between randomization and cut-off date, and follow-up times for PFS, which are defined as follows:
  - Randomization (recruitment) period = (Date of last patient randomized - Date of first patient randomized + 1) / 30.4375 (months)
  - Duration between randomization and data cut-off date = (Cut-off date – Date of randomization + 1) / 30.4375 (months). This item will be summarized overall.
  - Follow-up time = (Date of event or censoring – Date of randomization + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as the last adequate tumor assessment date for PFS. This item will be summarized by treatment arm.

All summaries will be reported in months. The calculations for PFS will be based on local assessment. Date of censoring is the same as defined in the PFS analysis.

The time from PFS censoring date to data cut-off date will be summarized by time intervals in months: <3, 3 - < 6, 6 - < 12, 12 - < 18, 18 - <24 and by 12 month intervals thereafter if necessary. The gap time is calculated as ([analysis cut-off date] - [censoring date] + 1)/30.4375.

5.5 Confidence intervals for response rate and clinical benefit rate

Response rate and clinical benefit rate will be summarized as percentages with 95% confidence intervals. A standard Wald asymptotic confidence interval, i.e., normal approximation, (implemented using SAS procedure FREQ for one-way tables) will be calculated.

5.6 Imputation rules

The partial date imputation rule will be described in the programming datasets specification.

5.7 AEs coding/grading

5.7.1 Coding of AEs

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

5.7.2 Grading of AEs

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE v4.0.3 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death.

If CTCAE grading does not exist for an adverse event, grades 1 – 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE grade 5 (death) will also be used in this project; if an AE results in death it will be documented in the outcome ("fatal"). Information on deaths will also be collected on the 'Death' CRF.

5.8 Laboratory parameters derivations

Not applicable

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Appendix 1 CTC grades for laboratory values in Novartis Oncology

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010) **Page 1**

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9/L	< 3.0 – 2.0 x 10^9/L	< 2.0 – 1.0 x 10^9/L	< 1.0 x 10^9/L
WBC [2] (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9/L	-
Hemoglobin [2] (Anemia)	g/L	HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M)	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L	< 100 - 80 g/L < 6.2 - 4.9 mmol/L	< 80 g/L < 4.9 mmol/L	-
Hemoglobin ↑	g/L	HGB	*(16.113 x mmol/L = g/L)*		Increase >0-20 g/L above ULN	Increase >20-40 g/L above ULN	Increase >40 g/L above ULN	-
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9/L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9/L
Neutrophils [3]↓	10^9/L	NEUT		≥2x10^9/L	< 2.0 - 1.5 x 10^9/L	< 1.5 - 1.0 x 10^9/L	< 1.0 - 0.5 x 10^9/L	< 0.5 x 10^9/L
Lymphocytes [3]↓	10^9/L	LYM		≥1.5x10^9/L	< 1.5 - 0.8 x 10^9/L	< 0.8 - 0.5 x 10^9/L	< 0.5 - 0.2 x 10^9/L	< 0.2 x 10^9/L
Lymphocytes ↑	10^9/L	LYM			-	> 4 - 20 x 10^9/L	> 20 x 10^9/L	-
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase [4]↑	U/L	CK	**30 - 170 U/L** or 0.5 – 2.83 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Total Cholesterol ↑	mmol/L	CHOL	**3.88 – 5.15 mmol/L** or 150 - 199 mg/dL *(38.67 x mg/dL = mmol/L)*	≤ ULN	> ULN - 7.75 mmol/L > ULN - 300 mg/dL	> 7.75 -10.34 mmol/L > 300 – 400 mg/dL	>10.34-12.92 mmol/L > 400 – 500 mg/dL	>12.92 mmol/L > 500 mg/dL
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

LAB - CTC grades in Novartis Oncology (26Oct15)

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – June 2010) **Page 2**

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Phosphorus[2] (Hypophosphatemia)	mmol/L	PHOS	**0.97 – 1.45 mmol/L** or 3.0 - 4.5 mg/dL *(0.32 x mg/dL = mmol/L)*	≥ LLN	< LLN - 2.5 mg/dL < LLN - 0.8 mmol/L	< 2.5 - 2.0 mg/dL < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL < 0.6 - 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L
Calcium (corrected) [2] (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) [2] (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (non-fasting) [2] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [2] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose [2] (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [2] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [2] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [2] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [2] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Triglyceride [2] ↑	mmol/L	TRIG	**< 2.82 mmol/L** or < 250 mg/dL *(0.01129 x mg/dL = umol/L)*	< 150 < 1.71	≥ 150 - 300 mg/dL ≥ 1.71 – 3.42 mmol/L	> 300 - 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 - 1000 mg/dL > 5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L
Coagulation								
INR [2]↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time[2]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Fibrinogen [4]↓	g/L	FIBRINO	**1.5 – 3.5 g/L** or 150 – 350 mg/dL *(0.01 x mg/dL = g/L)*	≥ LLN	< LLN - 0.75 x LLN	< 0.75 - 0.5 x LLN	< 0.5 - 0.25 x LLN	< 0.25 x LLN

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.
(2) = **Life-threatening consequences and/or hospitalization are <u>not</u> considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.
(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, **≥ 1.5 x 10^9/L (lymphocytes) and ≥ 2 x 10^9/L (neutrophils) are considered as LAB CTC grade 0**
(4) = For Creatinine and Fibrinogen, the **comparison with baseline is <u>not</u> considered** for derivation of LAB CTC grades

LAB - CTC grades in Novartis Oncology (26Oct15)