Parexel International

EQRx, Inc.

Protocol Number: EQ132-201

A Phase 2 Study to Evaluate the Safety and Efficacy of Lerociclib in Participants with Advanced Breast Cancer

Statistical Analysis Plan

Version: 3.0

Parexel Project Number: 262558

SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	[redacted]

	Signatory
Sponsor	[redacted]

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	20DEC2021	New document
2.0	27FEB2023	Updated to add additional AE summaries, changed some subgroup analysis groups, differentiated exposure between IMP and non-IMP treatment, and clarified ECG summaries, TEAE definition, and study day; updated some TEAE summaries to be by study treatment; updated language for RECIST algorithm vs. investigator assessments; updated interim analysis language; updated to align with minor changes to DSMB SAP
3.0	02AUG2023	Updated disposition, added disease characteristics and cancer history to demographics and other baseline characteristics for summary, added overall compliance, added CTCAE lab shift summaries; added analysis visit windows

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
1L	First-line
2L	Second-line
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	Area under the curve
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CI	Confidence interval
CR	Complete response
CRF	Case report form
CS	Clinically significant
CSR	Clinical study report
CT	Computed tomography
CV	Coefficient of variation
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG Performance Status
eCRF	Electronic case report form
ED	Early discontinuation
EORTC-QLQ	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full Analysis Set
FDA	Federal Drug Administration
HER2-	Human epidermal growth factor 2-negative
HR+	Hormone receptor-positive
IB	Investigator's Brochure
ICF	Informed consent form

Abbreviation / Acronym	Definition / Expansion
IMP	Investigational Medicinal Product
mBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
NE	Not evaluable
NIMP	Non-investigational Medicinal Product
NK	Not known
Non-CR/non-PD	Non-complete response/non-progressive disease
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PR	Partial response
PT	Preferred term
QoL	Quality of Life.
QTcB	QT corrected by Bazett
QTcF	QT corrected by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
RE	Response evaluable
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTR	Time to response
WHO-DD	World Health Organization – Drug Dictionary

1 INTRODUCTION

This is a multicenter, single-arm, open-label study to evaluate the safety and efficacy of lerociclib administered in combination with standard endocrine therapy in female or male participants with hormone receptor-positive (HR+)/human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (mBC).

Cyclin-dependent kinase (CDK) 4/6 inhibition has been demonstrated preclinically to synergize with anti-estrogen therapy in breast cancer models, and subsequent clinical work has led to the FDA approval of 3 CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) in both newly diagnosed, treatment-naïve participants with HR+/HER2- mBC (collectively referred to as the first-line, or 1L, population) and participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole (collectively referred to as the second-line, or 2L, population). CDK 4/6 inhibitors are associated with known adverse events (AEs). The purpose of this study is to better identify those AEs in participants with 1L and 2L mBC. In addition, efficacy measurements will be collected.

This Statistical Analysis Plan (SAP) describes the analyses to be presented in the clinical study report (CSR). Pharmacokinetics and other clinical pharmacology analyses will be performed outside the scope of this SAP and summarized in the CSR.

Analyses outside the scope of this SAP will be performed as needed by the Investigators and Sponsor for purposes including but not limited to publication, responses to inquiries from regulatory agencies and other health authorities, planning of future studies, and exploration of medical resource utilization. When available at time of writing, important findings from these analyses will be summarized in the CSR.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol EQ132-201, Version 3.0 (Amendment 3) (February 27, 2023)

Regulatory guidance documents judged relevant for compliance purposes:

- ICH-E6
- ICH-E9

Important references:

- Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [1]

The complete listing of references is included in Section 5.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective is:

- To characterize the safety and tolerability of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC.

2.2 Secondary Objective(s)

The secondary objectives are:

- To investigate the efficacy of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC by line of therapy.
- To further characterize the safety and tolerability of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC.
- To assess change from baseline in global health status and quality of life (QoL) in participants with 1L and 2L HR+/HER2- mBC by line of therapy (1L and 2L).
- To characterize the pharmacokinetic (PK) profile of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC.

2.3 [redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multicenter, single-arm, open-label study to evaluate the safety and efficacy of lerociclib administered in combination with standard endocrine therapy in female or male participants with HR+/HER2- mBC.

The study population will consist of newly diagnosed, treatment-naïve participants with HR+/HER2- mBC (the 1L population) and participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole (the 2L population). All premenopausal or perimenopausal female participants, and all male participants, must be receiving goserelin for at least 28 days prior to entering the study and will remain on goserelin throughout the study, in accordance with the prescribing information and according to the study site's standard practice.

The study will consist of 3 phases: A Screening Phase of up to 42 days in duration; a Treatment Phase (which includes a Safety Follow-up Visit occurring 30 days after the last dose of lerociclib); and a Survival Follow-up Phase that will continue until participant death, loss of follow-up, withdrawal of consent, or the end of the overall study (whichever occurs first).

While receiving lerociclib, participants will undergo imaging assessments (via computed tomography [CT] of the chest/abdomen/pelvis with contrast or magnetic resonance imaging [MRI] with gadolinium) every 8 weeks for the first 12 months, then every 12 weeks thereafter. All participants will undergo a bone scan at baseline and annually thereafter (or as per the Investigator's standard of

care). If bone disease is identified, participants will require whole-body bone scans every 8 weeks for the first 12 months and then every 12 weeks thereafter.

Optional imaging modalities include a brain CT/MRI (if brain lesion[s] indicated at Screening), CT/MRI for any disease outside the chest/abdomen/pelvis (if lesion[s] identified at Screening), or skin color photography (if skin lesion[s] identified at Screening) every 8 weeks during the first 12 months, then every 12 weeks thereafter.

Participants will continue therapy until disease progression as determined by Investigator per RECIST v 1.1, unacceptable toxicity, withdrawal of consent, start of a new anticancer treatment, discontinuation of the participant by Investigator, or termination of the study by the Sponsor, whichever occurs first.

Following disease progression, participants will only be followed for survival, and will no longer require any scheduled assessments beyond that timepoint. Survival status will be assessed every 12 weeks regardless of the participant's reason for discontinuing study treatment.

3.1.1 Number of Participants

Approximately 100 participants will be enrolled and dosed in the study, with approximately 50 participants enrolled and dosed for each line of therapy (1L or 2L).

3.1.2 Intervention Groups and Duration

Lerociclib is administered as a 150 mg tablet, to be taken orally twice daily (BID).

Based on current available data, lerociclib may be administered without regard to food; however, dosing under fed conditions appeared to improve gastrointestinal tolerability. For this reason, as well as for consistency across the study population, participants in this trial will be advised to take lerociclib after eating.

All participants (1L and 2L populations) will receive an AI (letrozole) or fulvestrant plus lerociclib 150 mg BID. All participants should be treated according to the best current practice guidelines and standard of care within each institution or country where the study is conducted.

All study participants will continue therapy until disease progression (as determined by Investigator per RECIST 1.1), unacceptable toxicity, withdrawal of consent, start of a new anticancer treatment, discontinuation of the participant by Investigator, or termination of the study by the Sponsor, whichever occurs first. Following disease progression, participants will only be followed for survival, and will no longer require any scheduled assessments beyond that timepoint. Survival status will be assessed every 12 weeks regardless of the participant's reason for discontinuing study treatment.

Dose adjustments of lerociclib for toxicities are to be made according to the organ system showing the greatest degree of drug-related toxicity. Toxicities will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE v5.0).

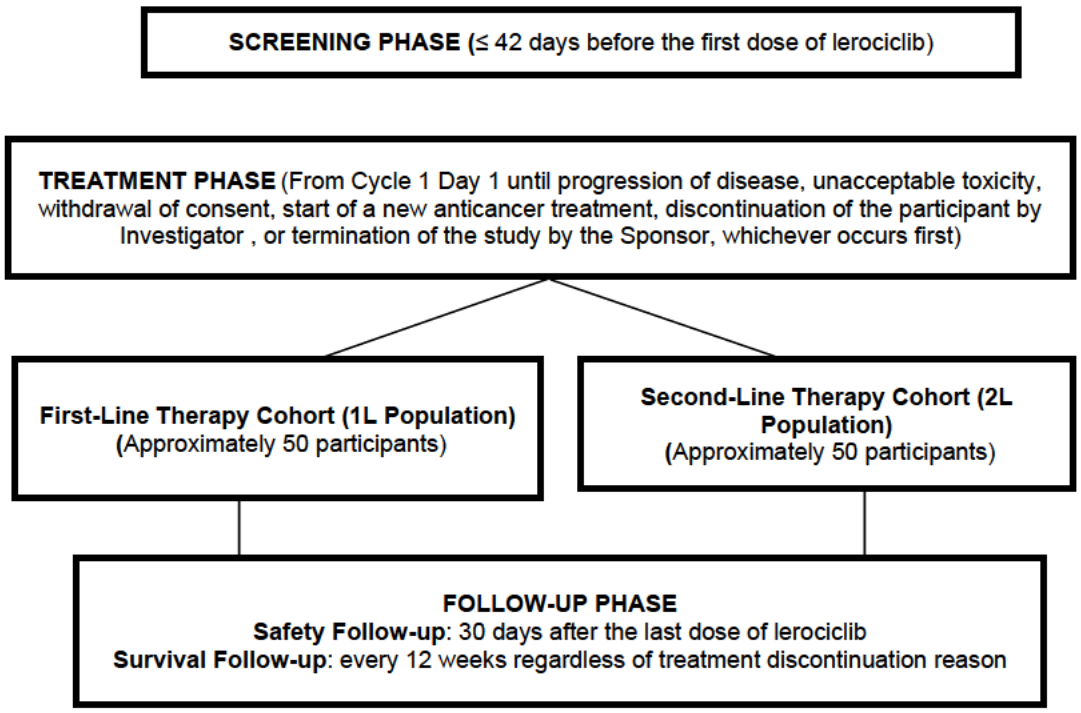
No more than two (2) lerociclib dose level reductions in total are allowed for any participant in this study. Any toxicity that requires reduction of a study participant's lerociclib dose level more than twice will result in permanent discontinuation of lerociclib dosing for the individual participant. No lerociclib dose re-escalations are allowed for any individual participant if the participant's dose reduction was due to a lerociclib-related toxicity. In cases where the relationship of the toxicity to lerociclib is unclear, the Investigator may re-challenge the participant after discussion with the Medical Monitor.

Lerociclib dose reduction will only be performed if the participant's symptom(s) is (are) related to lerociclib in the opinion of the Investigator, and not related to the participant's underlying disease.

The total study duration will be approximately 48 months. This assumes a duration of 12 months to complete participant recruitment and a median progression-free survival (PFS) duration of 24 months, plus an additional 12 months of survival follow-up for further monitoring. The full schedule of assessments is presented in Appendix 6.1.

An independent Data Safety Monitoring Board (DSMB) will be set up to periodically review and evaluate the accumulated study data for assessment of participant safety and study conduct and progress, and to make recommendations to the Sponsor concerning the continuation of the study.

Figure 3 Study Schema



Statistical analyses will be performed by line of therapy without formal comparisons between populations. [redacted]

3.2 Endpoints

The following endpoints will be used to evaluate the efficacy and safety of the study treatment based on the study objectives:

Objectives	Endpoints
Primary	
To characterize the safety and tolerability of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC.	• Incidence of adverse events (AEs) and serious adverse events (SAEs)
Secondary	

Objectives	Endpoints
To investigate the efficacy of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC by line of therapy.	• Objective response rate (ORR), defined as the proportion of participants with a best overall response of complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as assessed by Investigator • Clinical benefit rate (CBR), defined as the proportion of participants with a best overall response of CR, PR, or stable disease (SD) according to RECIST v1.1 as assessed by Investigator • Progression-free survival (PFS), defined as the time from first dose of lerociclib until the date of documented progression of disease (PD) or death, according to RECIST v1.1 as assessed by Investigator • Overall survival (OS), defined as the time from the date of first dose of lerociclib to the date of death due to any cause • Duration of response (DOR), defined as the time from the date of first documented response until the date of confirmed PD or death, according to RECIST v1.1 as assessed by Investigator • Time to response (TTR), defined as the time from first dose of lerociclib until the first documented response (CR or PR)
To further characterize the safety and tolerability of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC.	• Change from baseline in clinical laboratory parameters (hematology, clinical chemistry, coagulation, fasting lipid panel, and urinalysis) • Change from baseline in vital signs and 12-lead electrocardiogram (ECG) parameters • Clinically significant findings on physical examination
To assess change from baseline in global health status and quality of life (QoL) in participants with 1L and 2L HR+/HER2- mBC by line of therapy.	• Change from baseline in the Global Health Status/QoL Scale Score of the EORTC-QLQ-C30 • Change from baseline in the Global Health Status/QoL Scale Score of the EORTC-QLQ-BR23

Objectives	Endpoints
	• Change from baseline in the Global Health Status/QoL Scale Score of the EQ-5D-5L • Change from baseline in the Global Health Status/QoL Scale Score of the FACIT Item GP-5
To characterize the pharmacokinetic (PK) profile of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC.	• Predose and postdose concentrations of lerociclib for population PK (PopPK) analysis.
Exploratory	
[redacted]	[redacted]

3.2.1 Safety Variables

- AE assessments – recorded as they occur for the duration of the study
- Clinical laboratory parameters – measured at Screening, Day 1 of each cycle, Cycle 1 Day 15, and EOT/early discontinuation (ED)
- Vital sign parameters – measured at Screening, Day 1 of each cycle, Cycle 1 Day 15, and EOT/ED
- ECG parameters – measured at Screening, Day 1 of each cycle, Cycle 1 Day 15, and EOT/ED
- Physical examinations – measured at Screening, Day 1 of each cycle, and EOT/ED
- Concomitant medication assessments – recorded as they occur for the duration of the study

3.2.2 Efficacy Variables

- Tumor evaluation assessments – measured at Screening; every 8 weeks (± 7 days) during the first 12 months and every 12 weeks (± 7 days) thereafter until disease progression, death, withdrawal of consent, loss to follow-up, participant/legally acceptable representative decision; and at end of treatment (EOT) (If PR/CR is reported, confirmation of response is required; confirmatory assessment should be performed ≥ 4 weeks after response is first documented)
- Global Health Status/QoL Scale Scores (EORTC-QLQ-C30, EQ-5D-5L, and FACIT Item GP-5) – recorded at Screening; on Day 1 of each cycle (before any other study procedures) until disease progression, death, withdrawal of consent, loss to follow-up, participant/legally acceptable representative decision; and at EOT
- Global Health Status/QoL Scale Score EORTC-QLQ-BR23 – recorded at Screening; on Day 1 of every other cycle (before any other study procedures) until disease progression, death, withdrawal of consent, loss to follow-up, participant/legally acceptable representative decision; and at EOT

3.3 Pharmacokinetic Variables

- PK blood samples for concentrations of lerociclib – recorded pre and postdose at Day 1 and Day 15 of Cycle 1 and on Day 1 of Cycles 2, 3, 4, and 5.

The detailed procedures for the population PK and exposure-response analyses, including model development and evaluation, will be described in a Pharmacometric Analysis Plan.

3.4 [redacted]

[redacted]

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

Where appropriate, confidence intervals will be presented to one more decimal place than the raw data. All analyses will be performed by line of therapy.

4.2.1 Definitions

'Baseline' is defined as the last available pre-treatment assessment, where treatment includes the investigational medicinal product (IMP) or any non-investigational medicinal product (NIMP).

'End of Treatment' is defined as the value obtained at the EOT visit. If a value for a given parameter was not collected at the EOT visit the last available value collected prior to the EOT visit may be used.

'End of Study' (EOS) is defined as the last available post-treatment assessment.

'Study Day' will be calculated relative to the date of first exposure to lerociclib. For assessments prior to first exposure, Study Day = Assessment Date – Date of First Exposure. For assessments on or after first exposure date, Study Day = Assessment Date – Date of First Exposure + 1.

The timing of events may also be presented as the Cycle Number and Day (or CXDY), where X is the cycle number and Y is the number of days since the first day of lerociclib treatment in the cycle + 1.

4.2.2 Priority of Analyses

For each endpoint, one analysis will be identified as the "main" analysis of its evaluation. These analyses will be the basis upon which that endpoint will be evaluated. No formal hypothesis testing methods will be used.

Additional analyses of the information used in the main analysis such as subsets, covariate adjustments, and sensitivity analyses may be included in this analysis plan or added to the study report as needed. Such additional analyses may be added as separate tables/figures or have their results appended to the presentation of the main analysis and may also be presented in abbreviated forms.

4.2.3 Continuous Data

Continuous data will be summarized in terms of the mean, standard deviation, median, minimum, maximum, and number of observations, unless otherwise stated.

Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The

mean, median, confidence intervals, lower quartile, and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

4.2.4 Categorical Data

Unless otherwise specified for a given analysis, categorical data will be presented by the following rules. Categorical data not broken out by time (e.g., AE incidence) will be summarized in terms of the number of participants in the appropriate analysis set (n), frequency counts, and percentages. Categorical data broken out by time (e.g., ECOG PS by visit) will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the relevant section of this SAP as well as specifications for the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator as described above.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

4.2.5 Time-to-event Data

Descriptive summaries of time-to-event data will include median, twenty-fifth and seventy-fifth percentiles, and 95% confidence intervals (CIs) (where applicable) based on Kaplan-Meier methods.

4.3 Software

All report outputs will be produced using SAS® version 9.4 [2] or a later version in a secure and validated environment.

4.4 Study Participants

4.4.1 Disposition of Participants

A clear accounting of the disposition of all participants who enter the study will be summarized, from screening to study completion, including the following:

- The number of participants screened for entry into the study
- The number and percentage of participants excluded prior to first treatment
- The number and percentage of participants treated (with at least one dose of study medication)
- The number and percentage of participants in each analysis population
- The number and percentage of participants withdrawing from study treatment with primary reason
- The number and percentage of participants withdrawing from the study with primary reason

A by-participant listing of eligibility details will be produced, including visit dates, cycle numbers, date of withdrawal from treatment, date of withdrawal from study (including reason for discontinuation from treatment/study and duration of treatment/study participation).

4.4.2 Protocol Deviations

Major protocol deviations are defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. All major protocol deviations will be categorized and

summarized descriptively, as per data collected by protocol deviation tracking database. Protocol deviations will be presented for each participant in a by-participant data listing.

Prior to database lock, all protocol deviations will be reviewed and assigned a status of Major Deviation based on clinical or study judgement on their possible impact on study outcomes. As these data are not collected in CRF, if data format is not suitable for summary, only a data listing will be provided.

Protocol deviations and major protocol deviations will be categorized as noted in the Protocol Management Plan.

4.5 Analysis Sets

The following analysis populations will be used for presentation and analysis of data:

- Safety Analysis Set is defined as all enrolled participants who have received at least 1 dose of study intervention (IMP or NIMP).
- Full Analysis Set (FAS) is defined as all enrolled participants who were exposed to lerociclib (IMP) during the study.
- Response Evaluable (RE) Analysis Set is defined as all enrolled participants who were exposed to lerociclib during the study and who had measurable disease at baseline.

All safety analyses will be assessed using the Safety Analysis Set. PFS, OS and QoL will be assessed using the FAS. Tumor response endpoints will be assessed using the RE Analysis Set. As all participants are to receive the same treatment, all analyses will be summarized based on the planned treatment dose. Any deviations from planned treatment will be documented.

The FAS and Safety Analysis Set will be derived programmatically using study drug exposure data. The RE Analysis Set will be derived programmatically as determined by investigator assessment of baseline disease status using RECIST v1.1..

A summary of the number and percentage of participants by line of therapy for each analysis set will be presented.

A by-participant listing of analysis set details will be provided, including site, participant identifier, inclusion/exclusion flag for each set, and reason for exclusion from each set..

4.6 Demographic and Other Baseline Characteristics

Demographics to be summarized will include:

- Age (years)
- Assigned Sex at Birth (Female, Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White) with Subcategories (as collected on the CRF).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Country
- Childbearing Potential (Yes, No)

Baseline characteristics will include:

- Height (cm)

- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Target Lesions at Baseline (Yes, No)
- Non-target Lesions at Baseline (Yes, No)
- Measurable Disease at Baseline (Yes, No)

Disease History at Baseline and Cancer History will also be summarized.

Summaries of demographic and other baseline characteristics will be produced by line of therapy in the Safety Analysis Set.

A by-participant listing of demographic and baseline characteristics will be produced including participant identifiers, demographic and baseline variables, and line of therapy .

Age will be calculated as the number of complete years between a participant's birth date and the date of informed consent.

4.7 Prior and Concomitant Medications and Procedures

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior only. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication, then the medication will be classified as both Prior and Concomitant. Medications will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

Procedure dates will be compared to the date of first dose of study medication to allow medications to be classified as Prior or Concomitant.

Partial or missing dates will be imputed per rules outlined in Appendix 6.2.

All prior and concomitant medications/procedures will be coded using the latest version of WHO Drug Dictionary (WHO-DD) version (March 1, 2021 or higher).

Summaries will be produced of the number and proportion of participants with any prior and concomitant medications/procedures and for specific medications, including Anatomic Therapeutic Chemical (ATC) class 2 and preferred term (PT) by line of therapy. Participants taking more than one medication or having more than one procedure within the same ATC class 2 and PT will only be counted once.

By-participant listings of prior and concomitant medications will be produced with ATC level 2 and preferred term, including actual non-imputed start/stop dates, route, dose, frequency, and indication (Analysis Set: Safety Analysis Set). When the indication is an AE or medical history, the medical history or AE identifier will be listed.

By-participant listings of prior and concomitant procedures will be produced with ATC level 2 and preferred term, including procedure date(s), site, type of procedure, if oncological in nature, and if used to treat target or non-target lesions.

4.7.1 Subsequent Antineoplastic Cancer Therapy

Subsequent antineoplastic cancer therapy will be summarized.

A by-participant listing for subsequent antineoplastic cancer therapy will be produced.

4.8 Treatment Compliance

IMP and non-IMP treatment exposure/compliance will be monitored through dosing diaries in the eCRFs.

For each participant, dates of administration for each treatment are recorded on the corresponding Study Drug Administration eCRF forms. The start date of administration for the first entry will be considered the date of first dose of treatment, and the end date of administration for the last entry will be considered the last date of treatment.

If the date of last dose of study treatment is missing, ie, participant lost to follow-up, the last known drug administration date will be used to calculate duration of exposure.

Compliance with IMP and non-IMP treatments will be summarized.

For oral treatments (Lerociclib, Letrozole) and injection treatment (Fulvestrant), the compliance percentage will be summarized as:

[Total Dose (mg) Taken/Total of All Planned Doses (mg)]*100

Planned doses will account for any prescribed dose interruptions and modifications. Treatment compliance will be summarized for each treatment individually.

Compliance for injected treatment Goserelin cannot be calculated, as this is an implant that gradually releases total dose injected.

The number and percentage of participants who had at least one dose interruption will be provided. The number and percentage of participants with < 80%, 80% to 120%, and > 120% compliance will be provided by line of therapy for each visit. For all other compliance variables, compliance will be summarized by percentage for the whole exposure period.

The compliance variables will be listed in a by-participant listing.

4.9 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Analysis Set as defined in Section 4.5.

4.9.1 Adverse Events

4.9.1.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether considered related to the study intervention or not. See Appendix 3 of the protocol for full details of AE definition and classification.

4.9.1.2 Coding of Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. AE severity will be graded using NCI CTCAE v5.0.

4.9.1.3 Treatment-emergent Adverse Events (TEAEs)

Treatment-emergent adverse events (TEAEs) will be tabulated and are defined as those adverse events that either start or worsen in severity on or after the date/time of first dose of study treatment through 30 days after end of treatment or the day before initiation of a new antineoplastic treatment, whichever occurs first. Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment or after the Post-Treatment Follow-up visit. Partial dates will be imputed per rules outlined in Appendix 6.2.

An overall summary table will be created to present high level TEAE and treatment-related adverse event (TRAE) information. The following will be summarized (presenting the number of participants and number of events) by line of therapy, system organ class (SOC), and preferred term (PT):

- TEAEs
- TRAEs
- Serious TEAEs
- Serious TRAEs
- For each study treatment
    - TEAEs Leading to Drug Discontinuation
    - TEAEs Leading to Drug Reduction
    - TEAEs Leading to Drug Interruption
    - TEAEs Leading to Drug Reduction or Interruption

Additionally, the following summaries presenting the number of participants and number of events will also be created:

- TEAEs by line of therapy and PT
- TEAEs in >10% of participants by line of therapy and PT
- TRAEs by line of therapy and PT
- TEAEs by line of therapy, maximum severity grade, SOC, and PT (number of participants only)

Adverse event summaries will be ordered alphabetically for SOC, and decreasing frequency of PT within SOC for the total column (including both lines of therapy).

For each participant and each adverse event, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to Lerociclib) will be attributed and used in the by-causality summaries. If severity or causality is missing, a conservative approach for AE assessment (implementing the worst case) will be followed.

Adverse events of special interest (AESIs) TEAEs and TRAEs will also be summarized by line of therapy, maximum severity grade, SOC, and PT for the following terms:

AESI	Definition
Febrile neutropenia	MedDRA code #10016288
Pneumonitis	MedDRA code #10035742
Interstitial lung disease	MedDRA code #10022611

Note that if the PT or MedDRA code for any of these AESIs change in subsequent versions of MedDRA, this will not be considered a change to planned analysis.

By-participant listings of all TEAEs and serious TEAEs will be provided. These listings will be presented by line of therapy and will include center, participant identifier, age, sex, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, severity, seriousness, outcome, action taken (each treatment), and causality (each treatment).

4.9.2 Deaths

TEAEs resulting in death will be summarized by line of therapy, SOC, and PT.

Deaths will also be summarized by the number of deaths occurring in each line of therapy along with primary cause of death.

A listing of all deaths occurring during the study will be provided and will include center, participant identifier, age, sex, race, date of first treatment, date of last treatment, primary cause of death, on-treatment death (Yes/No), and autopsy performed (Yes/No).

4.9.3 Clinical Laboratory Evaluation

Chemical laboratory assessments include hematology, clinical chemistry, routine urinalysis, and pregnancy testing. The laboratory tests required by the protocol are detailed in Appendix 10.2 of the protocol.

All laboratory assessments will use local laboratories with results reported on the CRF. As such, laboratory assessments will be summarized by the visit in which the assessment was conducted.

For by-visit summaries, visit windowing will be implemented as specified in Section 4.10.1.3. For across visit summaries (e.g., worst post-baseline value), scheduled, unscheduled and repeat assessments will be considered.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. When there are repeat laboratory tests conducted on samples collected during the same visit, the last non-missing assessment will be summarized.

Laboratory values for hematology and clinical chemistry will be summarized as raw, change from baseline, and maximum change from baseline (for the participant). Descriptive statistics (for non-categorical data) will be presented by line of therapy for both raw values (n, mean, standard deviation, median, minimum, maximum) and changes from baseline.

A summary of the incidence of abnormal, high, or low values will be created by line of therapy and visit. Shift tables will be created for hematology and clinical chemistry parameters for which normal ranges exist. Shift tables for CTCAE grade shifts from baseline to worst post-baseline will also be presented by line of therapy for hematology and clinical chemistry for low and high shifts separately.

For urinalysis, a summary of the incidence of abnormal, high, and low values will be created. Shift tables will not be created for urinalysis.

A separate summary of findings of potential drug induced liver injury (DILI) will be prepared. The number and proportion of participants meeting one or both of the following criteria at any post-treatment visit will be summarized:

- ALT or AST 3 × ULN and total bilirubin 2 × ULN (> 35% direct bilirubin) or
- ALT or AST 3 × ULN and international normalized ratio (INR) > 1.5.

A figure for evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) will also be presented.

By-participant listings of all laboratory data will be provided, with treatment-emergent abnormal values identified (as appropriate), and including center, participant identifier, line of therapy, age, sex, race, and visit. The lab normal ranges will also be included, where available. Laboratory values summarized for a given visit will be labeled with the visit number and all other laboratory data will be listed as unscheduled.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with ‘L’ for values below the lower limit of the clinical reference range and ‘H’ for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs.

4.9.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs and ECGs will be summarized by line of therapy and timepoint.

The raw value and change from baseline will be summarized for vital sign parameters (weight, BMI, heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and temperature). Additionally, post-baseline shift summaries will be presented for temperature, SBP, DBP, and weight. For subjects with multiple records at a visit, the latest record will be summarized.

The raw value and change from baseline will be summarized for abnormal/CS records for ECG parameters (RR, PR, QRS, QT, QT corrected by Bazett [QTcB], and QT corrected by Fridericia [QTcF]) by line of therapy and visit/timepoint (for raw values and change from baseline). Note that ECG parameters are only recorded for a subject if the overall assessment is abnormal/CS, so only abnormal/CS parameter responses are summarized. ECGs are also collected in triplicate, so average values will be presented where multiple assessments are abnormal, clinically significant at a timepoint. Additionally, post-baseline shift summaries will be presented for heart rate, PR, QRS, and QTcF.

A by participant, by-visit listing of vital signs also will be produced.

A separate summary of the number and proportion of participants experiencing clinically significant abnormal ECG findings will be summarized, including the specific ECG abnormality, by line of therapy and visit/timepoint.

QTcF will be graded per CTCAE v5.0 grading criteria. A summary of the number and proportion of participants with any QTcF abnormalities, with Grade 3 or higher abnormalities, and with clinically significant Grade 1 and 2 abnormalities will be produced by line of therapy and visit/timepoint as well as overall (any timepoint). Abnormal and clinically significant ECG findings will also be reported through the AEs.

Additional summaries of the QTcF data may be performed, such as the number and proportion of participants with:

- Absolute QTcF interval prolongation:
  - QTcF interval $\geqslant$ 450 milliseconds
  - QTcF interval $\geqslant$ 480 milliseconds
  - QTcF interval $\geqslant$ 500 milliseconds
- Change from baseline in QTcF interval:
  - QTcF interval increases from baseline $\geqslant$ 30 milliseconds
  - QTcF interval increases from baseline $\geqslant$ 60 milliseconds

By-participant, by-timepoint listings of ECG parameters will be produced including raw values, change from baseline, normal ranges, abnormal flags, and clinical significance flags.

Clinically significant physical examinations will be reported as AEs as specified in the protocol.

4.9.5 Extent of Exposure

Descriptive statistics (n, mean, standard deviation, median, and range) will be used to summarize the following derived lerociclib exposure variables for each participant in each treatment group. Summaries will be by line of therapy.

- Time on Treatment (days): date of last dose – date of first dose + 1 day,
- Total dose (mg) Received: the sum of total mg taken during the total duration of exposure,
- Average Dose per Day (mg/day): actual cumulative dose intake / total duration of exposure
- Relative Dose Intensity: the amount received divided by the total amount expected on study based in intended dose and time on treatment

Two lerociclib dose level reductions in total are permitted for each participant before discontinuation. The following will be summarized for lerociclib by line of therapy:

- Number and percent of participants with dose interruptions
- Number and percent of participants with a dose reduction
  - Number and percent of lowest daily dose level (200 mg, 150 mg) for each participant requiring a dose reduction
- Number of treatment discontinuations

4.9.6 Data and Safety Monitoring Board (DSMB)

Analyses to be performed in support of the DSMB will be conducted in accordance with the DSMB charter under a separate analysis plan.

4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

Hypothesis testing or other inferential statistical methods will not be used for main analyses of the primary and secondary endpoints.

4.10.1.1 Handling of Dropouts or Missing Data

Data will be presented as observed unless otherwise specified.

Completely or partially missing dates will be imputed per rules outlined in Appendix 6.2.

4.10.1.2 Multiple Comparisons/Multiplicity

No adjustments for multiplicity are required.

4.10.1.3 Visit Windows

Analysis visit windows will be created based on the schedule of assessments in the protocol (Appendix 6.1) as shown below. Any visits outside the visit window will be considered "Unscheduled" and not summarized at a scheduled visit. If multiple records are mapped to the same visit, the one closest to the date of the scheduled assessment will be used. If there is an equal distance from the date of the scheduled assessment, the latest record will be used.

Visit	Study Day Window
Screening	[-42, -1]
Cycle 1 Day 1	1
Cycle 1 Day 15	[13, 17]
Cycle 2 Day 1	[27, 31]
…	[expected day – 2 days, expected day + 2 days]
EOT/ED	[last dose day, last dose + 15 days]
Safety Follow-up	[last dose + 25 days, last dose + 35 days]

For tumor evaluations, the following windows will be implemented:

Visit	Study Day Window
Screening	[-42, -1]
Cycle 3 Day 1	[50,64]
Every 2 cycles (8 weeks) during first 12 months and every 3 cycles thereafter (12 weeks) until EOT/ED	[expected day – 7 days, expected day + 7 days]
EOT/ED	[last dose day, last dose + 15 days]

4.10.1.4 Interim Analyses

No interim analyses are planned for this study.

4.10.1.5 Examination of Subgroups

The uniformity of the treatment effect for the efficacy analysis of Progression-Free Survival (PFS) will be examined for the following subgroups:

1. Age at Enrollment
2. Ethnicity (Not Hispanic or Latino, Other)
3. Race (White, Other)
4. Sex (Female, Male) – – While males are allowed in the study it is expected that their enrollment will be very limited. The CSR will note any occurrences when the enrollment of males is too low to allow analyses to run.
5. Childbearing Potential (Yes, No)
6. For Non-Childbearing Potential (Premenarchal, Surgically Sterile, Postmenopausal, Other)
7. Geographic Region
8. Age at Initial Diagnosis
9. Stage at Initial Diagnosis
10. Age at Most Recent Diagnosis
11. Metastasis Sites (Nervous System, Bone, Liver, Respiratory System, Adrenal Gland, Brain, Breast, Other) – may be categorized
12. Histology (Epithelial of ductal origin, Epithelial of lobular origin, Other)
13. Initial Cancer Type [Ductal carcinoma in situ (DCIS), Lobular carcinoma in situ, Invasive ductal carcinoma (ductal breast cancer), Invasive lobular carcinoma, Medullary carcinoma, Mucinous (colloid) carcinoma, Tubular carcinoma, Papillary carcinoma, Metaplastic breast cancer (mBC), Phyllodes tumors, Mammary Paget disease (MPD), Inflammatory breast cancer] – may be categorized
14. Stage at Study Enrollment
15. Reason for Discontinuation of Most Recent Prior Therapy (Progressive Disease, Toxicity, Completion, Unknown, Other, Specify)

Summaries of PFS by line of therapy and subgroup will be produced. No formal statistical analysis will be performed within subgroup.

4.10.2 RECIST Overall Response

The primary evaluation of efficacy endpoints will be based on the final assessment of timepoint Overall Response.

Extent of disease and tumor response will be assessed using Overall Response at each timepoint RECIST v1.1 (Eisenhauer 2009) as assessed by the Investigator (refer to Section 8.1.1 of the protocol). An Overall Response at each timepoint will be derived algorithmically based on the data entered for Target Lesions, Non-Target Lesions, and New Lesions. However, the Investigator can override this determination based on their clinical judgment of the participant at time of evaluation. In such cases the result of the RECIST algorithm will take precedence in the primary evaluation. The effect of any Investigator overrides will be explored as a sensitivity analysis.

. For participants with measurable disease at baseline the following timepoint responses are possible:

- Progressive Disease (PD)
- Stable Disease (SD)
- Partial Response (PR)
- Complete Response (CR)
- Not Evaluable (NE)

For participants who do not have measurable disease at baseline the following timepoint responses are possible:

- Progressive Disease (PD)
- Non-Complete Response / Non-Progressive Disease (Non-CR/Non-PD)
- Complete Response (CR)
- Not Evaluable (NE)

Once a RECIST v1.1 timepoint response of PD is observed all subsequent RECIST evaluations will not be used in analysis unless otherwise specified [redacted]

The primary evaluations of tumor response (ORR, CBR, DOR, and TTR) will be based on the RE set, which is limited to participants with measurable disease at baseline. [redacted]

4.10.2.1 Confirmation of Response

Unless otherwise specified analyses of response will be based on confirmed response. Confirmation of an initial response (CR or PR) requires observation of an equal or better response, following adequate follow up time defined as $\geq$ 28 days, without intervening PD.

4.10.3 Efficacy Analyses

4.10.3.1 Objective Response Rate (ORR) and Clinical Benefit Rate (CBR)

The ORR defined as the percentage of participants achieving a confirmed CR or confirmed PR based on RECIST, Version 1.1.

Unless otherwise specified all analyses of ORR will be based on the best overall confirmed response. “Best response” is defined according to the following hierarchy:

1) CR
2) PR
3) SD/ Non-CR/Non-PD
4) PD
5) NE

The CBR is defined as the percentage of participants having achieved a confirmed CR, confirmed PR, or SD (for at least 24 weeks ± 7 days).

The confirmed Best Overall Response, ORR, and CBR will be summarized by line of therapy along with the associated 2-sided exact 95% CIs based on the Clopper-Pearson method.

A forest plot of confirmed ORR by subgroup will be presented. Additionally, a swim lane plot as well as a table/waterfall plot showing the maximum percent change in target lesion reduction for each subject will be presented.

A by-participant listing of the best overall response data with ORR and CBR will be provided.

In addition, separate listings will also be provided for Target Lesions, Non-Target Lesions, and New Lesions for which these response assessments are conducted.

4.10.3.2 Progression-free Survival (PFS)

Progression-Free Survival (PFS) is defined as the time to PFS event from first exposure to lerociclib. PFS event is defined as PD (per RECIST v1.1 as assessed by the investigator) or death due to any cause, whichever comes first. For participants without death or disease progression, PFS will be censored at the date of the last valid RECIST assessment unless otherwise stated. PFS duration will be calculated as

Date of observation – Date of first exposure to lerociclib + 1

where date of observation is the earliest of death, progression, or censoring.

PFS events and censoring rules, such as initiation of disallowed anticancer therapy, are defined below in Table 2.

All valid RECIST assessments after start of treatment will be used in the PFS analysis regardless of whether they were collected as part of scheduled or unscheduled visits. RECIST assessments based on scans performed after the end of lerociclib therapy will be used in the analysis of PFS if prior censoring events have not been observed.

Table 2 Censoring Rules for Progression-Free Survival

Situation	Outcome	Date of Event/ Censoring
PD or death, whichever occurred first, before exposure to subsequent antineoplastic therapy, withdrawal of consent, loss to follow up, data cutoff, or end of study.	Event	Earliest date of documented progression or death
No baseline disease assessment	Censor	Date of first exposure
No valid post-baseline tumor assessment	Censor	Date of first exposure
PD or death immediately after missing ≥2 consecutive scheduled tumor assessment	Censor	Date of last valid tumor assessment prior to the missing tumor assessments
No PD or death on or before • Database cut • End of study • Start of new antineoplastic therapy	Censor	Date of last tumor assessment on or prior to earliest censoring event listed in first column of this row.

Descriptive summaries of time to event data will include median, twenty-fifth and seventy-fifth percentiles, and associated 2-sided 95% CIs based on Kaplan-Meier methods. Survival estimates along with corresponding 95% CIs using the log-log transformation will be provided at certain intervals as data allows.

A Kaplan-Meier plot will be presented and will include the number of participants at risk over time by line of therapy. No formal statistical hypothesis will be tested.

4.10.3.3 Overall Survival (OS)

OS is defined as the time to death by any cause from first exposure to lerociclib. Participants who have not died will be censored at the last contact date at which the participant is known to be alive.

Descriptive summaries of time to death data will include median, twenty-fifth and seventy-fifth percentiles, and associated 2-sided 95% CIs based on Kaplan-Meier methods. Overall survival estimates along with corresponding 95% CIs using the log-log transformation will be provided at certain intervals.

A Kaplan-Meier plot of the survival distribution will be presented and will include the number of participants at risk over time by line of therapy. No formal statistical hypothesis will be tested.

4.10.3.4 Duration of Response (DOR)

Only participants who have a confirmed response will be included in the analysis of DOR. DOR is defined as the time to PFS Event from first confirmed response. DOR will start at the time of the initial response and not the time for the confirmatory scan.

The definition of the end of DOR is the same as PFS Event, and the censoring rules will be the same as shown in Table 2 above.

Descriptive summaries of time to event data will include median, twenty-fifth and seventy-fifth percentiles, and associated 2-sided 95% CIs based on Kaplan-Meier methods.

A Kaplan-Meier plot will be presented and will include the number of participants at risk over time by line of therapy. No formal statistical hypothesis will be tested.

4.10.3.5 Time to Response (TTR)

Only participants who have a confirmed response (CR or PR) will be included in the analysis of TTR. TTR is defined as the time from first exposure to lerociclib to first confirmed response.

Descriptive summaries of time to response data will be presented.

4.11 Other Analyses

4.11.1 Pharmacokinetics

The detailed procedures for the pharmacokinetic endpoints will be described in a separate Pharmacometric Analysis Plan.

4.11.2 Patient Reported Outcome (PRO) Measures

Health-related quality of life (HR-QoL) will be assessed using the following measures:

- EORTC-QLQ-C30
- EORTC-QLQ-BR23
- EQ-5D-5L
- FACIT Item GP-5

4.11.2.1 EORTC QLC-C30 and EORTC QLQ-BR23

The EORTC-QLQ-C30 was developed to assess HR-QoL, functioning, and symptoms in cancer clinical trials. It consists of 30 questions, which can be grouped to produce five multi-item functional scales, three multi-item symptom scales, six individual items (five items assessing additional symptoms commonly reported by cancer patients and one item on the financial impact of the disease), and a two-item global measure of health status/quality of life:

- Functional scales:
    - Physical functioning
    - Role functioning
    - Emotional functioning
    - Cognitive functioning
    - Social functioning
- Multi-item symptom scales:

  - Fatigue
  - Nausea and vomiting
  - Pain
- Individual items:
  - Dyspnoea
  - Insomnia
  - Appetitive loss
  - Constipation
  - Diarrhoea
  - Financial difficulties
- Global health status/quality of life

The EORTC QLQ-BR23 is a breast cancer-specific module used to assess breast cancer-specific HR-QoL. It comprises 23 questions which can be grouped into five multi-item scores (body image, sexual functioning, arm symptoms, breast symptoms, and systemic therapy side effects) and single items on sexual enjoyment, upset by hair loss and future perspective. This instrument can be combined in four functional scales and four symptom scales:

- Functional scales:
  - Body image
  - Sexual functioning
  - Sexual enjoyment
  - Future perspective
- Symptom scales
  - Systemic therapy side effects
  - Breast symptoms
  - Arm symptoms
  - Upset by hair loss

An outcome variable consisting of a score from 0 to 100 will be derived for each of the functional scales, symptom scales, individual items, and global health status/ QoL in the EORTC QLQ-C30 and for each of the functional and symptom scales for the EORTC QLQ-BR23 according to the EORTC QLQ-C30 Scoring Manual and EORTC QLQ-BR23 instructions.

Higher scores on the global health status/QoL and functioning scales indicate better health status/functioning. Higher scores on the symptom scales indicate greater symptom burden.

For all scales, if at least half the components of a scale are present for a timepoint then the score will be calculated, otherwise the score will be set to missing.

The principle for scoring the scales of the QLQ-C30 and QLQ-BR23 are:

- Estimate the average of the items that contribute to the scale (raw score)

- Use a linear transformation to standardize the raw score, so that the scores range from 0 to 100

In practical terms, if terms $I_1, I_2, \ldots, I_n$ are included in a scale, then:

$$RS = \frac{\sum_{i=1}^{n} I_i}{n}$$

where RS denotes the raw score.

All functional scales are then calculated as $S = \left\{1 - \frac{RS-1}{range}\right\} * 100$ and symptom scales, items, and global health status as $S = \left\{\frac{RS-1}{range}\right\} * 100$.

Range is defined as the difference between the maximum possible value of RS and minimum possible value of RS for the specified scale.

The global health status/QoL, functional scales, and symptom scales, including the items included in each of these scales, are presented in Table 3 and Table 4.

Table 3 Scoring the QLQ-C30

	Scale	Number of Items	Item	Item Numbers
Global Health Status				
Global Health Status	QL2	2	6	29, 30
Functional Scales				
Physical	PF2	5	3	1 – 5
Role	RF2	2	3	6, 7
Emotional	EF	4	3	21 – 24
Cognitive	CF	2	3	20, 25
Social	SF	2	3	26, 27
Symptom Scales/Items				
Fatigue	FA	3	3	10, 12, 18
Nausea & Vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

a. Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

Table 4 Scoring the QLQ-BR23

	Scale	Number of Items	Item	Item Numbers
Functional Scales				
Body image	BRBI	4	3	9 – 12
Sexual functioning[d]	BRSEF	2	3	14, 15
Sexual enjoyment[b,d]	BRSEE	1	3	16
Future perspective	BRFU	1	3	13

Symptom Scales/Items				
Systemic therapy side effects	BRST	7	3	1 – 4, 6 – 8
Breast symptoms	BRBS	4	3	20 – 23
Arm symptoms	BRAS	3	3	17 – 19
Upset by hair loss[c]	BRHL	1	3	5

a. Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.
b. Not applicable if item 15 is "not at all".
c. Not applicable if item 4 is "not at all".
d. Items for these scales are scored positively (ie, "very much" is best) and therefore use the same scoring methodology as for symptom scales.

For all EORTC QLQ-C30 and BR23 scores, a clinical meaningful change or difference in score will be defined as a change of at least 10 points [3]. Specifically, a clinically meaningful improvement in a symptom will be defined as a decrease in the score from baseline of $\geqslant$ 10, whereas a clinical meaningful deterioration will be defined as an increase in the score from baseline of $\geqslant$ 10. In contrast, a clinical meaningful improvement in a functional scale or global health status/ QoL score will be defined as an increase in the score from baseline of $\geqslant$ 10, while a clinically meaningful deterioration in a functional scale or global health status/ QoL will be defined as a decrease in the score from baseline of $\geqslant$ 10.

Descriptive statistics for subscale scores, including changes from baseline, will be presented by visit and line of therapy. Plots of mean change from baseline in total and subscale scores over time will also be presented with indicators for the number of patients at each visit.

In addition, the proportion of patients experiencing improvement, no change or worsening from baseline will be presented by visit and line of therapy. Improvement, no change, and worsening will be defined as shown in Table 5 for all subscales.

Table 5 Change from Baseline Classification (EORTC QLC-C30, EORTC QLQ-BR23)

Score	Change from Baseline	Visit Response
Symptom scales/items	Change $\geq +10$	Worsened
	Change ≤ -10	Improved
	Otherwise	No Change
Functional scales and global health status/QoL	Change $\geq +10$	Improved
	Change ≤ -10	Worsened
	Otherwise	No Change

4.11.2.2 EQ-5D-5L

The EQ-5D-5L is comprised of six questions that cover 5 dimensions of health:

- Mobility
- Self-care
- Usual Activities
- Pain/Discomfort
- Anxiety/Depression

For each dimension, patients select which statement describes their health on that day from a possible five options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems). A unique EQ-5D health state, termed the EQ-5D-5L profile, is reported as a five-digit code with a possible 3,125 health states. For example, state 11111 indicates no problems on any of the five dimensions.

Patients will also assess their current health using the EQ-VAS which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

The EQ-5D profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the EQ-5D-5L profile that represents the comparative value of health states. The equation is based on national valuation sets elicited from the general population, and the base case will be the United Kingdom perspective. Where a valuation set has not been published, the EQ-5D-5L profile will be converted to the EQ-5D index using a crosswalk algorithm [4]. If an EQ-5D-5L value set does not exist for a country and neither does the EQ-5D-3L value set for use with the crosswalk algorithm, then a value set for a country that most closely resembles the country missing will be used.

Results from the EQ-5D-5L will be summarized descriptively by visit, including a shift table from baseline to worst on treatment for each dimension of health. Worst on treatment is defined as the highest numerical state for each dimension scored while on treatment (e.g., 2 is worse than 1). Plots of mean change from baseline in EQ-VAS and health state utility value over time will also be presented with indicators for the number of patients at each visit.

4.11.2.3 FACIT Item GP-5

FACIT Item GP-5 assesses the level to which each participant is bothered by side effects of treatment. It is a single score on a 5-point scale ranging from “not at all [bothered]” (0) to “Very much [bothered]” (4).

Results from the FACIT Item GP-5 will be summarized descriptively by visit, including a shift table from baseline to worst on treatment. Worst on treatment is defined as the highest numerical state while on treatment (e.g., 4 is worse than 3).

Plots of mean change from baseline value over time will also be presented with indicators for the number of patients at each visit.

4.11.3 Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

[redacted]

4.12 Determination of Sample Size

Approximately 100 participants will be enrolled and dosed in the study with approximately 50 participants in each line of therapy (1L or 2L). Assuming at least 80% of participants have measurable disease, approximately 40 of the planned 50 participants will have measurable disease per line of therapy. This sample size will allow an estimate of ORR with the half width of the 95% CI of no larger than approximately 16%.

4.13 Changes in the Conduct of the Study or Planned Analysis

This SAP is based on the Study EQ132-201 protocol Version 3.0, Amendment 3, dated February 27, 2023. This amendment is considered substantial, based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. However, it does not significantly impact analysis endpoints or methodology.

In addition, no changes to the statistical methods detailed in the study protocol have been implemented in this document.

5 REFERENCES

[1] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

[2] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright ©2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[3] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality of life scores. J Clin. Oncol. 1998; 16:139-144.

[4] van Hout B, Janssen MF, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health 2012; 15(5):708-15.

6 APPENDIX

6.1 Schedule of Assessments

Procedure	Screening	Treatment Phase						Post-Treatment Follow-up Phase	
		Cycle 1		Cycle 2	Cycle 3	Subsequent Cycles	EOT/ED (as applicable)	Safety Follow-up	Survival Follow-up Phase
Study Day(s)	**D-42 to D-1**	**D1**	**D15**	**D1**	**D1**	**D1**	**Within 15 days after last dose of lerociclib**	**Last dose of lerociclib + 30 days**	**Every 12 weeks**
Visit Window (days)	-	-	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	-	**+ 5 days**	**± 7 days**
Informed consent	X								
IRT participant number assignment (after ICF signature)	X								
Participant ID card distribution		X							
Inclusion/exclusion criteria	X	X							
Demography	X								
Medical history and current medical conditions (including details on cancer diagnosis, extent of cancer, and prior anticancer therapy)	X								
Estrogen receptor, progesterone receptor, and HER2 status	X								

Procedure	Screening	Treatment Phase						Post-Treatment Follow-up Phase	
		Cycle 1		Cycle 2	Cycle 3	Subsequent Cycles	EOT/ED (as applicable)	Safety Follow-up	Survival Follow-up Phase
Study Day(s)	**D-42 to D-1**	**D1**	**D15**	**D1**	**D1**	**D1**	**Within 15 days after last dose of lerociclib**	**Last dose of lerociclib + 30 days**	**Every 12 weeks**
Visit Window (days)	-	-	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	-	**+ 5 days**	**± 7 days**
Current line of endocrine therapy for mBC	X								
Prior medications review (including prior antineoplastic therapy)	X								
Concomitant medications review		X (continuous)						X	
Physical examination	X	X[a]		X[a]	X[a]	X[a]	X		
Height	X								
Body weight	X	X		X	X	X	X		
ECOG PS	X	X		X	X	X	X		
Clinical laboratory tests (hematology, clinical chemistry, coagulation, fasting lipid panel, and urinalysis)	X[b]	X[c]	X[c]	X[c]	X[c]	X[c]	X		
Pregnancy test[d]	X[b]	X							

Procedure	Screening	Treatment Phase						Post-Treatment Follow-up Phase	
		Cycle 1		Cycle 2	Cycle 3	Subsequent Cycles	EOT/ED (as applicable)	Safety Follow-up	Survival Follow-up Phase
Study Day(s)	**D-42 to D-1**	**D1**	**D15**	**D1**	**D1**	**D1**	**Within 15 days after last dose of lerociclib**	**Last dose of lerociclib + 30 days**	**Every 12 weeks**
Visit Window (days)	-	-	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	-	**+ 5 days**	**± 7 days**
FSH measurement (female participants only)	X								
12-lead ECG[e]	X[b]	X	X	X	X	X (at Cycles 4 and 5 only)	X		
ECHO or MUGA with EF		As clinically indicated by Investigator							
Vital signs	X	X	X	X	X	X	X		
PK sampling[f]		X	X	X	X	X (at Cycles 4 and 5 only)			
Tumor evaluation (per RECIST v1.1)	X	Every 8 weeks (± 7 days) during the first 12 months and every 12 weeks (± 7 days) thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or participant/legally acceptable representative decision, and at EOT/ED (as applicable). If PR/CR is reported, confirmation of response is required; confirmatory assessment should be performed ≥ 4 weeks after response is first documented.[1]							

Procedure	Screening	Treatment Phase						Post-Treatment Follow-up Phase	
		Cycle 1		Cycle 2	Cycle 3	Subsequent Cycles	EOT/ED (as applicable)	Safety Follow-up	Survival Follow-up Phase
Study Day(s)	**D-42 to D-1**	**D1**	**D15**	**D1**	**D1**	**D1**	**Within 15 days after last dose of lerociclib**	**Last dose of lerociclib + 30 days**	**Every 12 weeks**
Visit Window (days)	-	-	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	-	**+ 5 days**	**± 7 days**
Whole-body bone scan[g]	X	Every 8 weeks (± 7 days) for the first 12 months, then: -If initial bone scan is positive for bony lesion, every 12 weeks thereafter, OR -If initial bone scan is negative for bony lesion, bone scan can be done annually or per Investigator standard of care.							
Lerociclib administration		Twice daily continuously in 28-day cycles[h]							
Letrozole administration[i]		Once daily continuously in 28-day cycles							
Fulvestrant administration[i]		X	X	X	X	X			
Goserelin administration[j]	X	X		X	X	X			
AE/SAE review	X (continuous from Screening through 30 days after last study intervention dose)								
PROs: EORTC-QLQ-C30 (version 3), EQ-5D-5L, FACIT Item GP 5	X[b]	On Day 1 of each cycle (before any other study procedures) until disease progression, death, withdrawal of consent, loss to follow-up, or participant/legally acceptable representative decision, and at EOT.							
PRO: EORTC-QLQ-BR23	X[b]	On Day 1 of every other cycle (before any other study procedures) until disease progression, death, withdrawal of consent, loss to follow-up, or participant/legally acceptable representative decision, and at EOT.							

Procedure	Screening	Treatment Phase						Post-Treatment Follow-up Phase	
		Cycle 1		Cycle 2	Cycle 3	Subsequent Cycles	EOT/ED (as applicable)	Safety Follow-up	Survival Follow-up Phase
Study Day(s)	**D-42 to D-1**	**D1**	**D15**	**D1**	**D1**	**D1**	**Within 15 days after last dose of lerociclib**	**Last dose of lerociclib + 30 days**	**Every 12 weeks**
Visit Window (days)	-	-	**± 2 days**	**± 2 days**	**± 2 days**	**± 2 days**	-	**+ 5 days**	**± 7 days**
Collection of information on new anticancer therapies, as applicable							X	X	X
Survival follow-up									X[k]

a. A physical examination is to be performed on Day 1 of every cycle. According to Investigator's judgment, this can be an abbreviated physical examination.
b. To be performed between Day -7 and Day -1.
c. Results of clinical laboratory tests (hematology, clinical chemistry, coagulation, fasting lipid panel, and urinalysis) must be available prior to the administration of lerociclib on Day 1 of each cycle and on Day 15 of Cycle 1. Clinical laboratory tests may be obtained up to 24 hours prior to the scheduled visit.
d. For female study participants who are WOCBP (as defined in Protocol Appendix 4) only: Serum ß-hCG pregnancy test will be performed at Screening. Serum or urine ß-hCG pregnancy test will be performed at Cycle 1 Day 1 before the administration of the first dose of lerociclib. Beyond this timepoint, pregnancy test(s) may be performed at the discretion of the Investigator.
e. Participants will receive 12-lead ECGs (triplicate) at pre-dose and at 2 hours and 6 hours (± 10 minutes) after their lerociclib dose on Day 1 and Day 15 of Cycle 1, and then on Day 1 of Cycles 2, 3, 4, and 5. Triplicate 12-lead ECGs shall be obtained within a 5-minute period and shall be performed prior to blood draws whenever applicable. The same make and model of ECG machine should be used within each participant. In addition to triplicate 12-lead ECGs, a single 12-lead ECG will be collected (prior to blood draws) at Screening and at the EOT/EOD Visit. Other than at the EOT/EOD Visit, ECGs will not be conducted beyond Cycle 5 unless clinically indicated.
f. Pre-dose and post-dose blood samples for lerociclib concentration measurement are to be collected prior to and following the dose of lerociclib on Day 1 and Day 15 of Cycle 1, and on Day 1 of Cycles 2, 3, 4, and 5. The post-dose blood sample can be collected between 2 hours and 6 hours (± 10 minutes) after the administration of lerociclib. It is important to record the actual time of collection. If the participant is due for a 2- or 6-hour 12-lead ECG assessment, the PK sample may be drawn at the same timepoint but should be obtained after the ECG.
g. Radionuclide bone scans shall be performed at Screening for all participants every 8 weeks (± 7 days) for the first 12 months and every 12 weeks thereafter if initial bone scan is positive for bony lesion. If initial bone scan is negative for bony lesion, bone scan should be done annually or as clinically indicated per Investigator standard of care.

All participants with a CR must have a radionuclide bone scan as part of confirmation of the CR. Additional bone scans may be obtained at the discretion of the Investigator, if clinically indicated. Participants with bone-only disease may be followed only with bone scans at the discretion of the Investigator. If CT or bone scan have been done for regular clinical care within 28 days before receiving the first dose of lerociclib, these may be used as baseline scans.

h. Subsequent cycles may be postponed up to 14 days due to lerociclib interruption.

i. Participants in the 1L and 2L populations will receive the Investigator's choice of letrozole 2.5 mg daily or fulvestrant 500 mg (dosed according to schedule specified in the protocol).

j. All premenopausal or perimenopausal female participants, and all male participants, must be receiving goserelin for at least 28 days prior to entering the study and will remain on goserelin throughout the study, in accordance with the prescribing information and according to the study site's standard practice. For all study participants (female or male) receiving goserelin, their treatment with goserelin must start at least 28 days before their first dose of lerociclib.

k. After the Safety Follow-up Visit, survival follow-up should be attempted every 12 weeks for each participant in the long-term Survival Follow-up Phase. Follow-up can be performed via telephone, clinic visits, or by receiving information from a family member or another provider who is administering care. Any anticancer therapies used will be collected where possible.

l. CT or MRI scans obtained prior to informed consent will not need to be repeated if performed within 28 days prior to dosing with lerociclib.

Abbreviations: AE = adverse event; ß-hCG = human beta chorionic gonadotrophin; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperation Oncology Group performance status; ED = early discontinuation; EF = ejection fraction; EQ-5D-5L = EuroQoL 5-dimension 5-level; EORTC-QLQ = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EOT = end of treatment; FACIT= Functional Assessment of Chronic Illness Therapy; FSH = follicle-stimulating hormone; HER2 = human epidermal growth factor receptor 2; ICF = informed consent form; ID = identification; IRT = interactive response technology; mBC = metastatic breast cancer; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PK = pharmacokinetic(s); PR = partial response; PRO = patient-reported outcome; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event; WOCBP = women of childbearing potential.

6.2 Imputation Rules for Partial or Missing Dates

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of concomitant medication, start date of subsequent therapy, and death date. If dates are completely missing, no imputation will be made. For any partial date with missing year, no imputation will be made.

The general rule for imputation is:

- If only day is missing, then the 15th of the month will be used.
- If only year is present, then June 30th will be used.

If such imputation date for diagnosis is on or after date of first dose, the date of first dose – 1 will be used.

If such imputed date for subsequent therapies is before date of last dose, the date of last dose + 1 will be used.

If the imputed date is for an AE start date and is in the same year and month as the first dose date but before the first dose date, the first dose date will be used, or if the imputed AE start date is after the AE end date, the AE end date will be used.

If the imputed date is for an AE start date and is in the same year and month as last dose date + 30 days but after the last dose date + 30 days, the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, the death date will be used, or if the imputed AE end date is before the AE start date, the AE start date will be used.

For the missing death dates, if death year and month are available but day is missing:

- If mmyyyy for last contact date still alive = mmyyyy for death date, set death date to the day after the last contact date.
- If mmyyyy for last contact date still alive < mmyyyy for death date, set death date to the first day of the death month.

If both month and day are missing for death date or a death date is entirely missing, do not impute and censor the participant survival time.