



CLINICAL STUDY PROTOCOL

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

Compound: EQ132

Trade Name: Lerociclib

Indication: Advanced breast cancer

Study Sponsor: EQRx International, Inc.
50 Hampshire Street
Cambridge, MA 02139 USA

Protocol Number: EQ132-201

Study Phase: 2

Regulatory Agency Identifying Numbers: US: IND 154651
NCT05085002
EU: EudraCT 2021-005238-40

Protocol Version and Date: 3.0 (Amendment 3), 27 February 2023

CONFIDENTIALITY STATEMENT

This document contains confidential information, which should not be copied, referred to, released, or published without written approval from EQRx International, Inc. Background information provided in this protocol is subject to change and revision.

SPONSOR SIGNATORY

As a representative of the Sponsor, EQRx International, Inc., I confirm that this study protocol was subjected to critical review. The information contained herein is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the relevant law and any amendments thereof and in the current ICH Guidelines on GCP.

I confirm that the following protocol has been agreed to and accepted. The Sponsor will collect the signed Investigator's Agreement page of the protocol, in which each Investigator agrees to conduct the trial in compliance with the approved protocol and adhere to the principles outlined in the current ICH GCP Guidelines and any subsequent amendments thereof; the Sponsor's (and any other relevant) standard operating procedures; and all applicable regulatory requirements in the countries where the study is conducted and any subsequent amendments thereof.

I also confirm that the Sponsor will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay, and that an honest, accurate, and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

2/28/2023

Date

INVESTIGATOR'S AGREEMENT

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

All documentation for this study that is supplied to me and has not previously been published will be kept in the strictest confidence. Documentation includes, but is not limited to, the study protocol, Investigator's Brochure(s), electronic case report forms, and other scientific data.

The study will not commence without Approvals and/or registrations required in the countries where the study is conducted. No changes will be made to the study protocol without the prior written approval of the Sponsor, IRB/IEC, and all other applicable approvals as required in the countries where the study is conducted, except where necessary to avert an immediate hazard to the study participants.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current ICH GCP Guidelines and any subsequent amendments thereof; the current Guideline for GCP E6 (R2) (European Medicines Agency/Committee for Medicinal Products for Human Use/ICH/135/1995) and any subsequent amendments thereof; the current clinical trial regulations in the countries where the study is conducted and any subsequent amendments thereof; the Sponsor's (and any other relevant) requirements; and all applicable regulatory requirements in the countries where the study is conducted and any subsequent amendments thereof. The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1): Guideline for GCP ICH E6 (R2) and any subsequent amendments thereof.

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigational Site

Printed Name of Investigator

Signature of Investigator

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

| DOCUMENT HISTORY | |
|---|------------------|
| Document Version | Date |
| Version 3.0 (Amendment 3 [global; substantial]) | 27 February 2023 |
| Version 2.2 (Amendment 2.2 [Italy-specific; substantial]) | 24 Oct 2022 |
| Version 2.1 (Amendment 2.1 [Belgium-specific; substantial]) | 25 Apr 2022 |
| Version 2.0 (Amendment 2 [substantial]) | 10 Nov 2021 |
| Version 1.1 (Amendment 1 [nonsubstantial]) | 02 Sep 2021 |
| Version 1.0 (Original Protocol) | 27 Jul 2021 |

Version 3.0 (Amendment 3): 27 February 2023

Version 3.0 (Amendment 3) is considered to be a substantial protocol amendment because it involves substantive updates to the study contraception guidance, as well as updates to other safety information, and thus involves changes in the conduct/management of the study.

The overall rationale for updating to protocol Version 3.0 (Amendment 3) is the adoption of additional contraception and pregnancy testing requirements in accordance with the “Recommendations related to contraception and pregnancy testing in clinical trials” of the HMA Clinical Trial Facilitation Group ([CTFG 2020](#)).

Wherever applicable in the Summary of Changes table, deleted text is shown in ~~strikethrough~~ and added text is shown in **bold underlining**.

Note: Administrative updates to Version 3.0 of the protocol have also been made for improved clarity, consistency, and organization of content. These changes are not summarized in the table below, but are reflected in the redline version of the protocol.

| Section #(s), Title(s) | Description of Change | Brief Rationale |
|--|--|--|
| Global | <ul style="list-style-type: none"> Updates to templated protocol language and presentation of content have been made where applicable. | <ul style="list-style-type: none"> Providing consistency with the Sponsor's most current protocol template |
| Global | <ul style="list-style-type: none"> References to schedule for administration of goserelin have been updated so that each participant who is receiving goserelin upon entering the study will continue on their individual every-28-day cycle. For administration of goserelin only, dosing is de-coupled from the remainder of the study visit schedule, and "goserelin CID1" is determined as the date of the participant's last goserelin administration + 28 days. | <ul style="list-style-type: none"> Ensuring optimal convenience for each individual participant receiving goserelin in the study |
| Global | <ul style="list-style-type: none"> Sponsor name has been updated from "EQRx, Inc." to "EQRx International, Inc." where applicable. | <ul style="list-style-type: none"> Reflecting updated corporate name |
| 1.1, Synopsis 3, Objectives and Endpoints | <ul style="list-style-type: none"> Deleted "clinically significant findings on clinical examination" from secondary endpoints within Synopsis and Section 3 | <ul style="list-style-type: none"> Aligning with the Sponsor's updated protocol template language to reflect that physical examination forms are not included in the Sponsor's EDC |
| 1.3, Study SoA | <ul style="list-style-type: none"> Pregnancy testing frequency for female participants of childbearing potential has been increased to monthly throughout their time on study treatment. Pregnancy testing for female participants of childbearing potential who remain on study treatment has been specified as occurring during in-person study visits. Recording of pregnancy status has been added as a follow-up assessment to be performed during remote visits after female participants of childbearing potential have completed, or discontinued, study treatment. | <ul style="list-style-type: none"> Reflecting the assumption of the highest possible risk category for the early stages of human pregnancy, as reproductive and developmental toxicity studies with lerociclib have not yet been conducted Noting that pregnancy testing will be conducted while female participants of childbearing potential are attending the site, thereby allowing these participants to continue in the study Incorporating an additional consideration for female participants of childbearing potential who have completed, or discontinued, study treatment: they will not be required to return in person to the study site to complete a monthly pregnancy test, but will instead have their pregnancy status tracked remotely during post-treatment follow-up |
| 1.3, Study SoA | <ul style="list-style-type: none"> Estrogen receptor, progesterone receptor, and HER2 status (row was deleted) | <ul style="list-style-type: none"> Streamlining language. HR/HER2 status is part of the inclusion criteria and assessed as medical history |

| Section #(s), Title(s) | Description of Change | Brief Rationale |
|--|---|---|
| 1.3, Study SoA | <ul style="list-style-type: none"> Footnote “b” has been updated as follows: b To be performed between Day -7 and Day -1. <u>For safety laboratory collections, the Screening labs do not need to be repeated at CIDI if CIDI and Screening are within 7 days of each other.</u> | <ul style="list-style-type: none"> Minimizing participant and site burden during safety lab collections As outlined in Protocol Clarification Letter 1.1 (dated 01 June 2022) |
| 1.3, Study SoA 8.2.5, Pregnancy Testing | <ul style="list-style-type: none"> Statement has been added that in addition to serum β-hCG pregnancy testing conducted at Screening, serum or urine β-hCG pregnancy testing will also be performed at Day 1 of each cycle prior to administration of lerociclib, and may be performed at any other time during the study at Investigator discretion. | <ul style="list-style-type: none"> As noted above, reflecting the assumption of the highest possible risk category for the early stages of human pregnancy, as reproductive and developmental toxicity studies with lerociclib have not yet been conducted |
| 2.3.1, Benefit Assessment | <ul style="list-style-type: none"> <u>The benefits of lerociclib, a member of this class of drugs, has not yet been established.</u> | <ul style="list-style-type: none"> Updating for clarity |
| 4.4, End of Study Definition | <ul style="list-style-type: none"> Additional details and clarification were added to the definition of EOS, including that participants may be eligible for a long-term extension study of lerociclib. | <ul style="list-style-type: none"> Updating for clarity and adding availability of long-term extension study with lerociclib |
| 5.1, Inclusion Criteria 8.3.5, Pregnancy 10.4 (Appendix 4), Contraceptive and Barrier Guidance | <ul style="list-style-type: none"> Specification has been added that for female participants of childbearing potential, and male participants’ female partners who are of childbearing potential (as applicable), the duration of adherence to highly effective contraception measures is from 28 days prior to the first dose of any study intervention through at least 365 days (1 year) after the last dose of any study intervention. | <ul style="list-style-type: none"> Extending the period for required contraceptive measures to span the end of relevant systemic exposure |

| Section #(s), Title(s) | Description of Change | Brief Rationale |
|-------------------------|--|---|
| 5.1, Inclusion Criteria | <ul style="list-style-type: none"> Inclusion Criterion #9 has been updated as follows: 9. Must meet all of the applicable requirements for pregnancy and contraception, as follows: a. If female, is either: <ul style="list-style-type: none"> A WOCBP <u>participant of childbearing potential</u> (as defined in Appendix 4) who: OR A woman <u>participant of non-childbearing potential, as confirmed by meeting both of the following criteria who:</u> <ul style="list-style-type: none"> - <u>Has a negative serum pregnancy test result prior to the first dose of any study intervention, AND</u> - <u>Is confirmed by the Investigator to be medically postmenopausal per one or more of the following parameters:</u> <ul style="list-style-type: none"> ▪ <u>Age, in addition to any of the following:</u> ▪ <u>Menses status (ie, absence of menses for ≥ 1 year)</u> ▪ <u>Surgical status (ie, prior hysterectomy or bilateral oophorectomy)</u> ▪ <u>Follicle stimulating hormone level</u> <p>Is surgically sterile (by hysterectomy or oophorectomy) OR has been postmenopausal for ≥ 1 year and has a follicle-stimulating hormone (FSH) level ≥ 38 mIU/mL AND a negative serum pregnancy test result prior to the first dose of any study intervention, as noted in the SoA (Table 1); OR</p> <p>Is surgically sterile and provides documentation of the procedure (by operative report or ultrasound scan) prior to the first dose of any study intervention.</p> | <ul style="list-style-type: none"> For optimal Investigator flexibility and to minimize participant burden, in recognition that female participants confirmed as postmenopausal are included in the overall population for this study As outlined in Protocol Clarification Letter 1.1 (dated 01 June 2022) |
| 5.2, Exclusion Criteria | <ul style="list-style-type: none"> Exclusion Criterion #11 was updated to include evidence of active bacterial infection, fungal infection, or viral infection (including SARS-CoV-2 or uncontrolled HIV) | <ul style="list-style-type: none"> Aligning language across EQRx protocols |

| Section #(s), Title(s) | Description of Change | Brief Rationale |
|---|--|--|
| 6.2, Preparation, Handling, Storage, and Accountability | <ul style="list-style-type: none"> Only the pharmacist/designee and designated personnel will have access to the IMP (lerociclib), which must be stored at a temperature of 15°C to 30°C <u>Lerociclib tablets of all strengths are to be stored at the conditions specified in the EQ132-201 Pharmacy Manual</u> | <ul style="list-style-type: none"> Aligning with the most recent IB update and updating for additional IMP handling safety |
| 7.4, Criteria for Potential Stoppage (Permanent Discontinuation) of the Study | <ul style="list-style-type: none"> Details regarding potential stoppage criteria were deleted. | <ul style="list-style-type: none"> To enhance clarity for the Investigator/site and simplify the criteria |
| 8.3.6, Adverse Events of Special Interest (<i>section now deleted</i>) | <ul style="list-style-type: none"> Previously included AEFI section was deleted. | <ul style="list-style-type: none"> Reflecting that the two events previously referenced in this section, pneumonitis and interstitial lung disease, are part of the Reference Safety Information in the lerociclib IB and are not true AEFIs (rather, they are AEs of clinical interest). |

| Section #(s), Title(s) | Description of Change | Brief Rationale | | | | | | |
|--|---|---|------------|-------------------|--|--|---|---|
| 10.2 (Appendix 2), Safety Labs | <p>Table 9 has been updated as follows:</p> <p>Table 9: Protocol-required Safety Laboratory Tests</p> <table><tr><th>Laboratory Tests (as detailed in the SoA Table 11)</th><th>Parameters</th></tr><tr><td>Pregnancy testing</td><td>Highly sensitive serum or urine β-hCG pregnancy test (for WOCBP female participants of <u>childbearing potential</u> only; refer to Appendix 4) at timepoints detailed in the SoA (Table 1).</td></tr><tr><td>Other Screening tests (refer to the SoA Table 11)</td><td>Follicle-stimulating hormone and estradiol (as needed in female study participants of nonreproductive <u>childbearing</u> potential only) Fasting Lipid Panel (total cholesterol, low-density lipoprotein, triglycerides, high-density lipoprotein) Coagulation (prothrombin time/INR, partial thromboplastin time, D-dimer, fibrinogen)</td></tr></table> | Laboratory Tests (as detailed in the SoA Table 11) | Parameters | Pregnancy testing | Highly sensitive serum or urine β -hCG pregnancy test (for WOCBP female participants of <u>childbearing potential</u> only; refer to Appendix 4) at timepoints detailed in the SoA (Table 1). | Other Screening tests (refer to the SoA Table 11) | Follicle-stimulating hormone and estradiol (as needed in female study participants of non reproductive <u>childbearing</u> potential only) Fasting Lipid Panel (total cholesterol, low-density lipoprotein, triglycerides, high-density lipoprotein) Coagulation (prothrombin time/INR, partial thromboplastin time, D-dimer, fibrinogen) | <ul style="list-style-type: none">To clearly present the protocol-required safety lab collections in the context of the SoAAs outlined in Protocol Clarification Letter 1.1 (dated 01 June 2022) |
| Laboratory Tests (as detailed in the SoA Table 11) | Parameters | | | | | | | |
| Pregnancy testing | Highly sensitive serum or urine β -hCG pregnancy test (for WOCBP female participants of <u>childbearing potential</u> only; refer to Appendix 4) at timepoints detailed in the SoA (Table 1). | | | | | | | |
| Other Screening tests (refer to the SoA Table 11) | Follicle-stimulating hormone and estradiol (as needed in female study participants of non reproductive <u>childbearing</u> potential only) Fasting Lipid Panel (total cholesterol, low-density lipoprotein, triglycerides, high-density lipoprotein) Coagulation (prothrombin time/INR, partial thromboplastin time, D-dimer, fibrinogen) | | | | | | | |
| 10.4 (Appendix 4), Contraceptive and Barrier Guidance | <ul style="list-style-type: none">Specification has been added that male participants with female partners of childbearing potential are to use a condom throughout their study treatment through at least 365 days (1 year) after the last dose of any study intervention. | <ul style="list-style-type: none">Avoiding exposure of an existing embryo/fetus via seminal fluid, as reproductive and developmental toxicity studies with lerociclib have not yet been conducted | | | | | | |
| 10.4 (Appendix 4), Contraceptive and Barrier Guidance | <ul style="list-style-type: none">Specification has been added that for male participants receiving fulvestrant, the duration of adherence to highly effective contraception measures is during treatment with fulvestrant and for at least 365 days (1 year) after the last dose of fulvestrant. | <ul style="list-style-type: none">Clarifying the specific duration of contraception measures for male participants after the last dose of fulvestrant | | | | | | |

β -hCG = human beta chorionic gonadotrophin; CID1 = Cycle 1 Day 1; EDC = electronic data capture; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IB = Investigator's Brochure; IMP = investigational medicinal product; INR = international normalized ratio; SoA = schedule of activities; WOCBP = women of childbearing potential.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Sponsor Protocol Number: EQ132-201

Study Phase: 2

Sponsor: EQRx International, Inc.

Rationale:

The purpose of this study is to evaluate the safety and efficacy of lerociclib administered in combination with endocrine therapy in female or male participants with hormone receptor-positive (HR+)/human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (mBC).

Lerociclib is a potent and selective cyclin-dependent kinase (CDK) 4/6 inhibitor that in nonclinical models has been shown to effectively inhibit the growth of HR+ breast cancer in vitro and in vivo. Similar to other CDK4/6 inhibitors, lerociclib has been shown to act synergistically with endocrine therapies in nonclinical models. Specifically, this study will examine safety and tolerability of lerociclib administered in combination with Investigator's choice of endocrine therapy (aromatase inhibitor [AI] or fulvestrant).

The study population will consist of newly diagnosed 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). The study will also record clinical efficacy of lerociclib in combination with endocrine therapy.

Objectives and Endpoints:

| 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 | <ul style="list-style-type: none">Incidence of AEs and SAEs |
| Secondary To investigate the efficacy of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC by line of therapy | <ul style="list-style-type: none">Objective response rate, defined as the proportion of participants with a best overall response of CR or PR according to RECIST v1.1 as assessed by InvestigatorClinical benefit rate, defined as the proportion of participants with a best overall response of CR, PR, or SD (for at least 8 weeks) according to RECIST v1.1 as assessed by Investigator |

| Objectives | Endpoints |
|---|--|
| | <ul style="list-style-type: none"> • Progression-free survival, defined as the time from first dose of lerociclib until the date of documented PD or death, according to RECIST v1.1 as assessed by Investigator • Overall survival, defined as the time from the date of first dose of lerociclib to the date of death due to any cause • Duration of response, 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, 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 | <ul style="list-style-type: none"> • 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 ECG parameters |
| To assess change from baseline in global health status and QoL in participants with 1L and 2L HR+/HER2- mBC by line of therapy | <ul style="list-style-type: none"> • 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 • 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 PK profile of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC | <ul style="list-style-type: none"> • Predose and postdose concentrations of lerociclib for PopPK analysis |
| <div style="background-color: black; height: 15px; width: 100px; margin-bottom: 5px;"></div> <div style="background-color: black; height: 15px; width: 350px;"></div> | <ul style="list-style-type: none"> • <div style="background-color: black; height: 15px; width: 200px;"></div> |

1L = first-line population; 2L = second-line population; AE = adverse event; CR = complete response; ECG = electrocardiogram; EORTC-QLQ-BR23 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Breast; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EQ-5D-5L = EuroQoL 5-dimension 5-level questionnaire; FACIT Item GP-5 = Functional Assessment of Chronic Illness Therapy, physical wellbeing subscale, item 5 questionnaire; HER2- = human epidermal growth factor 2-negative; HR+ = hormone receptor-positive; mBC = metastatic breast cancer; PD = progression of disease; PK = pharmacokinetic(s); PopPK = population pharmacokinetic(s);

PR = partial response; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors;
SAE = serious adverse event; SD = stable disease.

Overall Design:

Brief Summary

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 schedule for administration of goserelin for each individual participant is decoupled from the rest of the study visit schedule, and will be determined by the date of the participant's most recent dose of goserelin at the time of study entry (with "goserelin C1D1" defined as the date of the participant's most recent dose + 28 days, then every 28 days subsequently).

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 Post-Treatment Follow-up Phase (which includes 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, then every 12 weeks thereafter.

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

Number of Participants:

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

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 study 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 the Investigator per RECIST v1.1), unacceptable toxicity, withdrawal of consent, start of a new anticancer treatment, discontinuation of the participant by the 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 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.

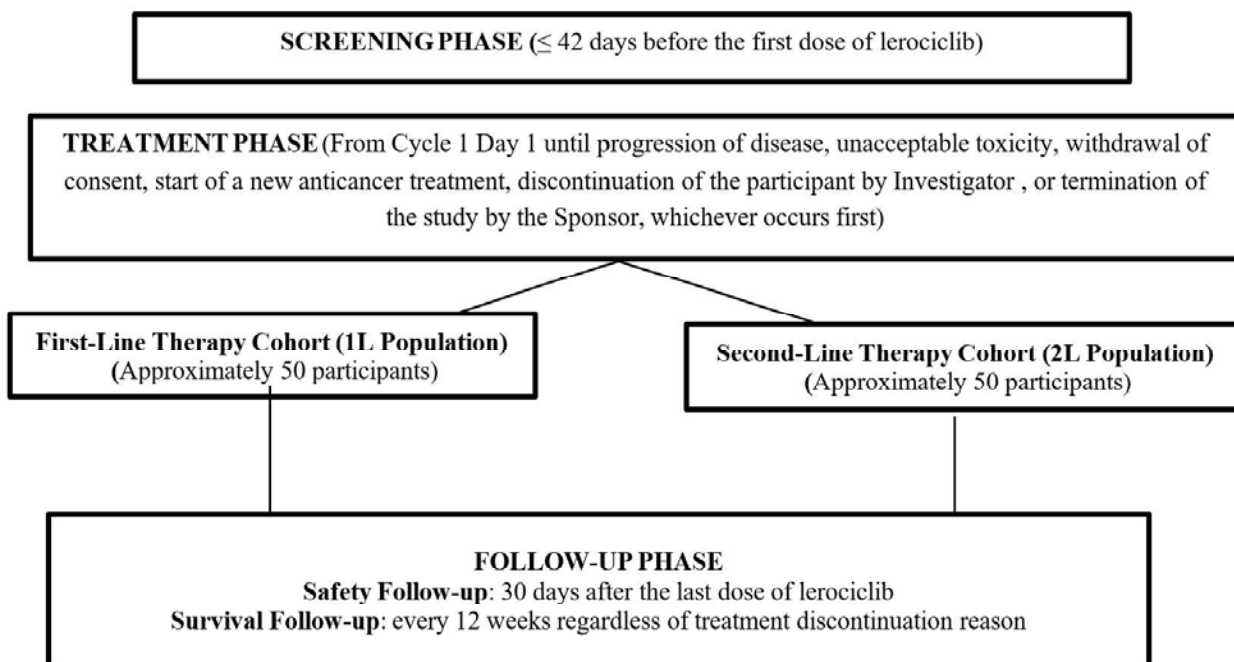
Lerociclib dose reduction will only be performed if the participant's symptom(s) is (are) related to lerociclib in the opinion of the Investigator, and not related to the participant's underlying disease.

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.

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.

1.2. Schema

Figure 1: Study Schema



1L = first-line; 2L = second-line.

1.3. Study Schedule of Activities

Table 1: Study SoA

| 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 | | | | | | | | |
| 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 | | |

| 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 |
| 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 | | X | X | X | | | |
| FSH Measurement (Female Participants of Non-Childbearing Potential 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 | | | | | | | |
| 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. | | | | | | | |

| 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 |
| Lerociclib Administration/Accountability | | Twice daily continuously in 28-day cycles ^a | | | | | | | |
| Letrozole Administration ⁱ | | Once daily continuously in 28-day cycles | | | | | | | |
| Fulvestrant Administration ⁱ | | X | X | X | X | X | | | |
| Goserelin Administration ^j | X (goserelin dosing required for ≥ 28 days prior to study entry) | X (determined as date of participant's last goserelin dose + 28 days ^l) | q28d after goserelin C1D1 for the individual participant | | | | | | |
| 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. | | | | | | | |
| Collection Of Information on New Anticancer Therapies and Pregnancy Status ^k , 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. For safety laboratory collections, the Screening labs do not need to be repeated at C1D1 if C1D1 and Screening are within 7 days of each other.
- 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 of childbearing potential (as defined in [Appendix 4](#)) only: Serum β -hCG pregnancy testing will be performed at Screening. Serum or urine β -hCG pregnancy testing will be performed at Day 1 of each cycle before the administration of lerociclib. At any timepoint during the study, pregnancy test(s) may be performed at the discretion of the Investigator.
- e. Participants will receive 12-lead ECGs (triplicate) at predose and at 2 hours and 6 hours (\pm 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/ED Visit. Other than at the EOT/ED Visit, ECGs will not be conducted beyond Cycle 5 unless clinically indicated.
- f. Predose and postdose 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 postdose blood sample can be collected between 2 hours and 6 hours (\pm 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 (\pm 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. Note that subsequent cycles should start on the original schedule (ie first dosing date).
- 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. The goserelin dosing schedule is decoupled from the rest of the study visit schedule, with each participant's "goserelin CID1" determined as the date of their most recent goserelin dose before entering the study + 28 days. Goserelin dosing will continue on a q28d basis throughout the participant's time on study. All of the participant's non-goserelin-dosing study activities are to occur as shown in the Schedule of Activities.
- 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 recorded where possible, as well as any changes to participant pregnancy status (as applicable).
- 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.
 β -hCG = human beta chorionic gonadotrophin; 1L = first-line; 2L = second-line; AE = adverse event; CR = complete response; CT = computed tomography; CID1 = Cycle 1 Day 1; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperation Oncology Group performance status; ED = Early Discontinuation; EF = ejection fraction; EORTC-QLQ-BR23 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Breast; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EOT = end of treatment; EQ-5D-5L = EuroQoL 5-dimension 5-level questionnaire; FACIT Item GP-5 = Functional Assessment of Chronic Illness Therapy, physical well-being subscale, item 5 questionnaire; FSH = follicle-stimulating hormone; 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; q28d = once every 28 days; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event.

2. INTRODUCTION

2.1. Study Rationale

Lerociclib is a novel CDK4/6 inhibitor with a promising efficacy and safety profile. Existing nonclinical and clinical data suggest lerociclib is highly efficacious for the treatment of HR+/HER2- mBC. The purpose of this study is to better characterize the safety profile of lerociclib in both 1L and 2L patients with HR+/HER2- mBC and gather additional efficacy data for lerociclib.

2.2. Background

The most common type of mBC globally is HR+/HER2- mBC. Estrogen deprivation, via anti-estrogens and AIs, have been established as the centerpiece of first- and second-line therapy for HR+/HER2- mBC. Letrozole is an orally bioavailable AI which is approved by the US FDA for women with mBC. Fulvestrant is an FDA-approved potent anti-estrogen drug that binds and degrades the ER. Cyclin-dependent kinase 4/6 inhibition has been shown to synergize with endocrine therapy (both AI and fulvestrant) and result in improvements in PFS and OS ([Cristofanilli 2016](#), [Finn 2016](#), [Sledge 2017](#), [Hortobagyi 2018](#), [Slamon 2018](#), [Slamon 2019](#), [Johnston 2019](#), [Spring 2019](#)). There are 3 FDA-approved CDK4/6 inhibitors: palbociclib, ribociclib, and abemaciclib. However, these molecules, despite their clinical efficacy, also have side effect profiles that are often challenging for participants, including nausea/vomiting, diarrhea, and hematologic toxicity (including neutropenia and leukopenia).

Lerociclib is a potent and selective CDK4/6 inhibitor that in nonclinical models has been shown to effectively inhibit the growth of HR+ breast cancer in vitro and in vivo. Likewise, in clinical exploration thus far, lerociclib has been shown to be efficacious and very well tolerated.

A detailed description of the chemistry, pharmacology, efficacy, and safety of lerociclib is provided in the lerociclib IB. A summary is presented below.

2.2.1. Summary of Nonclinical Data

A brief summary of the nonclinical data for lerociclib is provided in the following sections. Detailed information is provided in the lerociclib IB.

Lerociclib represents a novel class of orally bioavailable, competitive inhibitors of CDK4/6. These inhibitors prevent the CDK4/6-cyclin D complex from phosphorylating Rb, thus preventing the G₁ to S-cell cycle transition.

Primary pharmacology studies demonstrated that lerociclib produced a precise and reversible G₁ arrest in CDK4/6-dependent cells over a concentration range of 3 orders of magnitude in vitro. Lerociclib inhibited the phosphorylation of Rb at CDK4/6-specific sites with an average IC₅₀ of 30 nM as quickly as 16 hours after treatment. Collectively, nonclinical data demonstrate that lerociclib effectiveness requires functional Rb and has the potential to impact several tumor types.

Likewise, in vivo tumor models support the potential of lerociclib as a highly effective antineoplastic agent in a number of CDK4/6-dependent tumor types.

2.2.1.1. Nonclinical Pharmacokinetics

Lerociclib has high bioavailability in animals, with bioavailability in mice, rats, and dogs at approximately 60% to 90%. After repeated oral dosing in rats and dogs for 7 days or 28 days, systemic lerociclib exposures did not differ between male and female animals, showed little to no accumulation, and generally exhibited a slightly greater-than-dose-proportional increase.

The primary lerociclib metabolic products were formed by oxidative biotransformation, with G1T30, the product of oxidative N-dealkylation, being the predominant metabolite. In general, in vitro metabolite profiles were qualitatively similar in rats, dogs, and humans. Oxidative metabolism was mediated by CYP3A4 and CYP2C8. Lerociclib showed in vitro inhibition of CYP3A4/5 with a K_i of 15 μM and K_{inact} of 0.033 min^{-1} , but did not inhibit the other major human drug-metabolizing CYP isoforms, and did not significantly induce CYP1A2, CYP2B6, or CYP3A4 mRNA expression. Lerociclib was a substrate of P-gp and BCRP, and inhibited P-gp, BCRP, OCT1, OCT2, MATE1, and MATE2-K in cell models.

2.2.1.2. Nonclinical Toxicology

The toxicity of lerociclib was evaluated in repeat-dose studies in rats and dogs, as well as multiple in vitro genotoxicity studies. For further information, please refer to the lerociclib IB.

2.2.2. Summary of Clinical Data

Studies of lerociclib include the following:

- A first-in-human, single-dose, placebo-controlled Phase 1 study (G1T38-01) of lerociclib in healthy male and female participants. A total of 75 participants were dosed in this study and 57 participants were exposed to oral doses of lerociclib. Dosing started at 3 mg lerociclib and the highest dose administered was 600 mg lerociclib. The 600-mg total dose was explored as a single dose, as well as two 300-mg doses, each separated by 12 hours.
- A food effect, drug-drug interaction, and gastric pH study (G1T38-103) has also been completed in 19 healthy adult participants. Lerociclib was found to be well tolerated. Notably, food increased plasma lerociclib AUC_{0-t} , $\text{AUC}_{0-\text{inf}}$, and C_{max} by approximately 30% to 40% and caused an earlier t_{max} . Likewise, there was no impact on lerociclib PK by reduction of gastric pH by rabeprazole. Finally, co-administration of a strong CYP3A inducer (rifampin) significantly reduced lerociclib plasma concentrations. For this reason, it is recommended that co-administration of strong and moderate CYP3A inducers be avoided while taking lerociclib.
- A bioavailability and PK study was also completed in 22 participants to compare the capsule and tablet formulations of lerociclib (G1T38-06). Ultimately, it was found that the bioavailability of both lerociclib and its main metabolite G1T30 were comparable between the tablet and capsule formulations.

- In Study G1T38-03, 26 participants with EGFR-altered non-small cell lung cancer received escalating doses of lerociclib in combination with osimertinib 80 mg QD until disease progression or unacceptable toxicity. The primary outcome of the study was safety and tolerability of the combination. As a whole, lerociclib and osimertinib were generally well tolerated when dosed together. For full details of Study G1T38-03, please refer to the lerociclib IB.
- In Study G1T38-02 (ongoing), 110 participants with HR+/HER2- mBC who had progressed on at least 1 line of endocrine therapy were treated with increasing doses of lerociclib and 500 mg fulvestrant dosed intramuscularly. Ultimately, the recommended Phase 2 dose of lerociclib was found to be 150 mg BID. For full details of Study G1T38-02, please refer to the lerociclib IB.

2.2.2.1. Clinical Safety and Tolerability

In Study G1T38-01, single or BID oral doses of lerociclib in the dose range of 3 mg to 600 mg appeared to be safe and well to moderately tolerated in a group of healthy male and female participants. In most participants who demonstrated moderate tolerability, gastrointestinal AEs were the most common moderate-intensity TEAEs (as defined in Section 8.3).

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 study will be advised to take lerociclib after eating.

Effects on hematologic parameters were not observed with lerociclib due to the limited duration of dosing.

In Study G1T38-02, lerociclib was tolerated very well across several doses. The most common lerociclib-related AEs reported at 150 mg BID were neutropenia, leukopenia, diarrhea, and anemia. For further details, please refer to the lerociclib IB and DSUR.

2.2.2.2. Clinical Pharmacokinetics

Single-Dose Capsules

Following single-dose oral dosing in the fasted state, for the 48-mg dose level and beyond, lerociclib concentrations in plasma were quantifiable from the first (0.25 hour) or second (0.5 hour) postdose timepoint, with median t_{\max} increasing with increasing dose from 2 hours up to 6 hours postdose. After reaching peak concentrations, a multiphasic decline in plasma concentrations was observed. The geometric mean $t_{1/2}$ for single-dose lerociclib capsules was between 13.8 and 17.2 hours.

Effect of Food

Exploratory statistical analysis indicated a very small food effect (13%) on C_{\max} and no food effect on AUC_{0-t} or $AUC_{0-\infty}$ with lerociclib.

Twice-Daily Dosing

When the lerociclib daily dose was given divided over 2 equal doses, the median t_{\max} was 4 hours to 6 hours postdose following each dose. The geometric mean overall C_{\max} was lower following BID dosing than following the same total dose administered as a single dose.

Splitting the daily lerociclib dose over 2 doses resulted in similar or slightly lower total lerociclib plasma exposure (AUC_{0-t} and AUC_{0-inf}) compared to the same total daily dose given as a single administration.

Dose-Proportionality

Based on the dose-normalized PK parameter plots, both C_{max} and AUC values increased with dose in a more than dose-proportional manner at the lower doses (48 mg to 200 mg lerociclib), and in an approximately dose-proportional (AUC) or less than dose-proportional (C_{max}) manner over the dose range of 200 mg to 400 mg lerociclib.

Drug-Drug Interactions

Drug-drug interactions were explored in a total of 19 study participants. Use of the strong CYP3A inducer rifampin was found to significantly (by 82%) reduce the exposure of lerociclib. Based on this finding, concurrent use of strong CYP3A4 inducers should be avoided.

The use of the strong CYP3A inhibitor itraconazole was found to increase the lerociclib AUC by 40% and to increase C_{max} by 36%. However, the maximum tolerated dose of lerociclib is 500 mg QD. Therefore, no dosage adjustment is required for concurrent use of strong CYP3A inhibitors with the recommended lerociclib dose.

In a drug interaction study with a CYP3A4 substrate (midazolam), lerociclib was found to increase the AUC of midazolam by 28% and to increase C_{max} by 15% – thus indicating that lerociclib is a weak inhibitor of CYP3A4 in vivo. Although no clinically relevant interactions with CYP3A4 substrates are expected, caution remains advised with sensitive CYP3A substrates when co-administered with lerociclib.

Lerociclib had no effect on the PK of rosuvastatin, nor did it have any effect on the PK of digoxin.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of lerociclib can be found in the IB.

Lerociclib has been generally well tolerated so far. There was 1 SAR reported in a single participant in the ongoing Study G1T38-02. That participant experienced an SAR in the SOC of Respiratory, Thoracic and Mediastinal Disorders that included pneumonitis. The outcome of the SAR was recovered/resolved with supportive care. For full details, please refer to the lerociclib DSUR. Otherwise, there have been no other SAEs reported for other studies with lerociclib.

Toxicities anticipated in this study include interstitial lung disease/pneumonitis, neutropenia, thrombocytopenia, anemia, nausea/vomiting, diarrhea, and fatigue. As a whole, clinical experience thus far indicates that these toxicities are manageable and, if necessary, reversible with discontinuation of lerociclib.

Potential benefits of lerociclib treatment include a substantial improvement of clinical efficacy in combination with endocrine therapy (letrozole or fulvestrant) in patients with mBC. This benefit appears consistent with the magnitude of benefit seen with other CDK4/6 inhibitors.

2.3.1. Benefit Assessment

Benefits of CDK4/6 inhibitor therapy for patients with advanced/mBC appear to be substantial, with clear improvements in PFS and OS versus endocrine therapy alone. The benefits of lerociclib, a member of this class of drugs, has not yet been established.

Moreover, this study has no control arm, thereby allowing participants to receive lerociclib in combination with standard-of-care endocrine therapy.

2.3.2. Risk Assessment

Table 2: Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|--|---|
| ILD/pneumonitis | There is an identified increased susceptibility to ILD/pneumonitis. Please refer to the lerociclib IB and DSUR for full details. | ILD appears to be a rare side effect of CDK4/6 inhibitor therapy. While there are no known risk factors for the development of ILD, participants who demonstrate symptoms related to pneumonitis (cough, dyspnea, chest pain, fever) should be promptly evaluated and treated effectively. Holding of lerociclib is necessary if there is clinical concern for pneumonitis. Participants may require steroid administration, as well. |
| Febrile neutropenia | There is a small risk of the development of febrile neutropenia. | If a participant is suspected of febrile neutropenia, lerociclib should be held. Neutropenia from CDK4/6 inhibitors does not respond to G-CSF. Supportive care should be provided as clinically indicated while the participant's counts recover. Following the resolution of febrile neutropenia, a participant may continue lerociclib, with appropriate dose reduction as necessary. |
| Lerociclib | | |
| Neutropenia | Lerociclib has been demonstrated to cause a decline in neutrophil counts over the first 4–5 weeks of therapy. | Complications of neutropenia (infection, febrile neutropenia) are uncommon, and participants will be screened for potential complications at all study visits. |
| Gastrointestinal tolerability | Participants exposed to lerociclib commonly experienced transient diarrhea and nausea. | None of the TEAEs of diarrhea or nausea have been shown to be of Grade 4 or higher severity. Gastrointestinal side effects do respond to supportive therapy (anti-emetics, antidiarrheals). |

Table 2: Risk Assessment (Continued)

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|--|--|
| ILD/pneumonitis | Four of 140 study participants (2.9%) were diagnosed with ILD/pneumonitis based on clinical history and diagnostic findings. | Two study participants required hospitalization with no intensive care support. There were no fatal cases. There were no reports of ILD/pneumonitis in healthy participants. Caution should be taken for any participants with upper respiratory infection symptoms or dyspnea/hypoxemia. There should be a low threshold to re-image in such cases. |
| Study Procedures | | |
| Risk of excess radiation exposure due to CT scans. | CT scans have been shown to result in complications from excess radiation exposure. | CT scans will be conducted every 8 weeks for the first 12 months of the study, and are then spaced out to every 12 weeks to mitigate radiation exposure. |
| Other | | |
| Risk of arthralgia due to letrozole/fulvestrant/goserelin. | Letrozole/fulvestrant/goserelin have been shown to result in arthralgia in patients with mBC. | Each participant will be provided with information about signs and symptoms of arthralgia, hot flushes, and fatigue during the consent process; instructions on when to contact a healthcare provider; and relevant contact information. |
| Risk of hot flushes due to letrozole/fulvestrant/goserelin. | Letrozole/fulvestrant/goserelin have been shown to result in hot flush in patients with mBC. | |
| Risk of fatigue due to letrozole/fulvestrant/goserelin. | Letrozole/fulvestrant/goserelin have been shown to result in fatigue in patients with mBC. | |

CDK = cyclin-dependent kinase; CT = computed tomography; DSUR = development safety update report; G-CSF = granulocyte colony-stimulating factor; IB = Investigator's Brochure; ILD = interstitial lung disease; mBC = metastatic breast cancer; TEAE = treatment-emergent adverse event.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with lerociclib are justified by the anticipated benefits that may be afforded to participants with advanced breast cancer.

3. OBJECTIVES AND ENDPOINTS

Table 3: Study Objectives and Endpoints

| 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 | <ul style="list-style-type: none"> Incidence of AEs and SAEs |
| Secondary To investigate the efficacy of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC by line of therapy | <ul style="list-style-type: none"> Objective response rate, defined as the proportion of participants with a best overall response of CR or PR according to RECIST v1.1 as assessed by Investigator Clinical benefit rate, defined as the proportion of participants with a best overall response of CR, PR, or SD (for at least 8 weeks) according to RECIST v1.1 as assessed by Investigator Progression-free survival, defined as the time from first dose of lerociclib until the date of documented PD or death, according to RECIST v1.1 as assessed by Investigator Overall survival, defined as the time from the date of first dose of lerociclib to the date of death due to any cause Duration of response, 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, 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 | <ul style="list-style-type: none"> 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 ECG parameters |

Table 3: Study Objectives and Endpoints (Continued)

| Objectives | Endpoints |
|---|--|
| To assess change from baseline in global health status and QoL in participants with 1L and 2L HR+/HER2- mBC by line of therapy | <ul style="list-style-type: none"> • 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 • 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 PK profile of lerociclib in combination with endocrine therapy in participants with 1L and 2L HR+/HER2- mBC | <ul style="list-style-type: none"> • Predose and postdose concentrations of lerociclib for PopPK analysis |
| <div style="background-color: black; width: 100px; height: 1.2em; margin-bottom: 5px;"></div> <div style="background-color: black; width: 360px; height: 1.2em;"></div> | <ul style="list-style-type: none"> • <div style="background-color: black; width: 300px; height: 1.2em;"></div> |

1L = first-line population; 2L = second-line population; AE = adverse event; CR = complete response; ECG = electrocardiogram; EORTC-QLQ-BR23 = European Organisation for Research and Treatment of Cancer-Quality of Life-Questionnaire-Breast; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core; EQ-5D-5L = EuroQol 5 dimension 5 level questionnaire; FACIT Item GP 5 = Functional Assessment of Chronic Illness Therapy, physical wellbeing subscale, item 5 questionnaire; HER2- = human epidermal growth factor 2-negative; HR+ = hormone receptor-positive; mBC = metastatic breast cancer; PD = progression of disease; PK = pharmacokinetic(s); PopPK = population pharmacokinetic(s); PR = partial response; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease.

4. STUDY DESIGN

4.1. Overall Design

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 (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).

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). 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 schedule for administration of goserelin for each individual participant is decoupled from the rest of the study visit schedule, and will be determined by the date of the participant's most recent dose of goserelin at the time of study entry (with "goserelin C1D1" defined as the date of the participant's most recent dose + 28 days, then every 28 days subsequently).

All study participants (1L and 2L populations) will receive the Investigator's choice of 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.

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 Post-Treatment Follow-up Phase (which includes a Survival Follow-up Phase) that will continue until death, loss of follow-up, withdrawal of consent, or the end of the study (whichever occurs first).

While receiving lerociclib, participants will undergo imaging assessments (via CT of the chest/abdomen/pelvis with contrast or 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 the Investigator per RECIST v 1.1, unacceptable toxicity, withdrawal of consent, start of a new anticancer treatment, discontinuation of the participant by the 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.

Safety monitoring (AE/SAE monitoring, clinical laboratory tests, vital signs, 12-lead ECGs, physical examination), serial blood samples for PK, tumor biopsies, and bone scans will be performed at the timepoints specified in the study SoA ([Table 1](#)).

The study is anticipated to last for a total of approximately 48 months. This assumes 12 months to complete participant recruitment and a median PFS of 24 months, plus an additional 12 months for further monitoring.

An independent DSMB will be set up to periodically review and evaluate the accumulated study data for participant safety and for study conduct and progress, and to make recommendations to the Sponsor concerning the continuation of the study (as detailed in [Section 7.4](#)).

This study will be conducted in compliance with the protocol, GCP, and applicable regulatory and IRB/IEC requirements.

4.2. Scientific Rationale for Study Design

Cyclin-dependent kinase 4/6 inhibition has been demonstrated nonclinically to synergize with anti-estrogen therapy in breast cancer models, and subsequent clinical work has led to the FDA approval of 3 CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) in both 1L and 2L mBC.

CDK4/6 inhibitors are associated with known AEs. The purpose of this study is to better identify those AEs in participants with 1L and 2L mBC. Efficacy measurements will also be collected.

4.3. Justification for Dose

G1T38-02 was a Phase 1/2 study consisting of 2 parts: a dose-escalation phase (Phase 1) and a dose-expansion phase (Phase 2) of lerociclib in combination with fulvestrant in women with 2L HR+/HER2- mBC. A total of 110 female participants received lerociclib across doses of 200 mg to 650 mg QD and 100 mg to 250 mg BID.

The selected dose of lerociclib 150 mg BID demonstrated an improved tolerability profile relative to QD dosing and to all other BID doses, including improved rates of gastrointestinal AEs as well as lower rates of neutropenia.

Best overall response was comparable between the 150-mg BID dosing group and the 200-mg BID dosing group (CBR of 73.7% versus 70.7%). As such, 150 mg BID lerociclib was selected as the recommended dose.

Notably, of the participants treated with lerociclib 150 mg BID, Grade 4 neutropenia was reported in 1 participant, and no other lerociclib-related Grade 4 AEs were reported at that dose level. Grade 3 febrile neutropenia was also reported in 1 participant treated with lerociclib 150 mg BID. The most common Grade 3/4 AEs in participants treated with 150 mg BID were neutropenia (40%), leukopenia (20%), and lymphopenia (10%).

No lerociclib dose interruptions or reductions were required in any participant who experienced Grade 3 neutropenia without fever.

No lerociclib-related nausea, vomiting, or diarrhea event of Grade 3 or higher severity was reported in any participant treated with 150 mg BID.

Grade 2 stomatitis was reported in 1 participant treated with 150 mg BID. Grade 1 alopecia was reported in 1 participant treated with lerociclib 150 mg BID; this was the only alopecia event in the study.

The only lerociclib-related SAE reported in the 150-mg BID cohort was an episode of Grade 2 pneumonitis, which resolved with discontinuation of lerociclib. Lerociclib dose reduction occurred in 2 participants treated with 150 mg BID. No cases of QT prolongation or venous thromboembolism were reported at any dose level in the study.

4.4. End of Study Definition

The end of the overall study will be reached when all participants have ended their participation in the study. Participants may be eligible for a long-term extension study of lerociclib.

Additionally, the study may be placed on hold or terminated in any of the following circumstances:

- Overall, country-/region-specific, or site-specific study hold or termination by the Sponsor at any time, for any reason
- Study hold or termination in a specific country/region by the relevant Health Authority
- Study-site closure initiated by the IRB/IEC or by the Principal Investigator as detailed in Section [10.1.9.3](#)

Refer to Section [7.4](#) for additional information about potential study stoppage.

The Sponsor will notify the Investigators in the event of any study hold or termination, or in the event of overall study completion (defined as completion of the last study visit of the last participant in the study).

5. STUDY POPULATION

The study population will consist of female or male participants with newly diagnosed, treatment-naïve or post-first-line endocrine therapy HR+/HER2- mBC. All participants must be able to provide written consent and meet all of the study inclusion criteria and none of the study exclusion criteria.

Note: “Enrolled” in the context of a clinical study means the agreement of a participant to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Prospective participants are eligible to be included in the study only if **all** of the following criteria apply:

Informed Consent

1. Is capable of giving signed informed consent as described in Section 10.1.3. This includes compliance with the requirements and restrictions listed in the study ICF and in this protocol.

Age

2. Must be at least 18 years of age, or the legal age of consent in the jurisdiction in which the study is taking place, at the time of giving signed informed consent.

Type of Participant and Disease Characteristics

3. Has a histologically and/or cytologically confirmed diagnosis of ER-positive and/or progesterone receptor-positive breast cancer by local laboratory.
4. Breast cancer is also HER2-negative and advanced (locoregionally recurrent; not amenable to curative therapy, eg, surgery and/or radiotherapy; or metastatic) and meets one of the following criteria:
 - Newly diagnosed advanced/metastatic breast cancer, treatment-naïve
 - Relapsed with documented evidence of relapse following neoadjuvant (adjuvant) endocrine therapy, with no treatment for advanced/metastatic disease
 - Relapsed with documented evidence of relapse following completion of adjuvant endocrine therapy, then subsequently progressed with documented evidence of progression after 1 line of endocrine therapy (with either tamoxifen or an AI) for advanced/metastatic disease
 - Newly diagnosed advanced/mBC at diagnosis that progressed with documented evidence of progression after 1 line of endocrine therapy (with either tamoxifen, exemestane, or an AI)
5. Eastern Cooperative Oncology Group performance status is 0 or 1

6. Has adequate bone marrow and organ function, as defined by all of the following laboratory values:
 - Absolute neutrophil count $\geq 1.5 \times 10^9/\text{L}$
 - Platelets $\geq 100 \times 10^9/\text{L}$
 - Hemoglobin $\geq 9.0 \text{ g/dL}$
 - International normalized ratio ≤ 1.5
 - Creatinine clearance $\geq 60/\text{mL}$, as estimated by Cockcroft-Gault equation
 - Alanine aminotransferase and AST below $2.5 \times \text{ULN}$
 - Total bilirubin $\leq 1.5 \times \text{ULN}$; OR, for participants with well-documented Gilbert's Syndrome, direct bilirubin within normal range of the central laboratory
7. Baseline QTc interval is $< 470 \text{ msec}$.
8. Is able to take/swallow oral medications.

Sex and Contraceptive/Barrier Requirements

9. Must meet all of the applicable requirements for pregnancy and contraception, as follows:
 - a. If female, is either:
 - A participant of childbearing potential (as defined in [Appendix 4](#)) who:
 - Has a negative pregnancy test result at Screening and Cycle 1 Day 1 (ie, prior to the first dose of any study intervention), as noted in the SoA ([Table 1](#));
 - Is not breastfeeding;
 - Agrees to use highly effective contraceptive measures (as defined in [Appendix 4](#)) from 28 days prior to the first dose of any study intervention through at least 365 days (1 year) following the last dose of any study intervention, and to align contraceptive use with the relevant prescribing information for fulvestrant and/or goserelin, as applicable (refer to [Appendix 4](#)); AND
 - Agrees not to donate ova from the first dose of any study intervention through at least 1 year following the last dose of any study intervention.
 - OR
 - A participant of nonchildbearing potential, as confirmed by meeting both of the following criteria:
 - Has a negative serum pregnancy test result prior to the first dose of any study intervention, AND
 - Is confirmed by the Investigator to be medically postmenopausal per one of the following parameters:
 - Age, in addition to one of the following:
 - Menses status (ie, absence of menses for $\geq 1 \text{ year}$)

- Surgical status (ie, prior hysterectomy or bilateral oophorectomy)
 - Follicle-stimulating hormone level
- b. If male:
- Agrees to use a highly effective method of contraception (eg, male condom in addition to hormonal contraception; refer to [Appendix 4](#)) during intercourse with a female partner of childbearing potential from 28 days prior to the first dose of any study intervention through at least 365 days (1 year) following the last dose of any study intervention, and to align contraceptive use with the relevant prescribing information for fulvestrant and/or goserelin, as applicable ([Appendix 4](#)); AND
 - Agrees to refrain from donating sperm from the first dose of any study intervention through 1 year following the last dose of any study intervention.

Note: For all study participants, contraceptive use must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Refer to [Appendix 4](#) for additional guidance.

5.2. Exclusion Criteria

Prospective participants are excluded from the study if **any** of the following criteria apply:

Medical Conditions

1. Has symptomatic visceral disease or any disease burden that makes the participant ineligible for endocrine therapy, per the Investigator's best judgment.
2. Has peritoneal carcinomatosis.
3. Has inflammatory breast cancer at Screening.
4. Has CNS involvement, **unless** participant is at least 4 weeks from prior therapy completion to starting study treatment, has stable CNS tumor at the time of Screening, and is not receiving steroids and/or enzyme-inducing anti-epileptic medications for brain metastases.
5. Has any clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality.
6. Has a history of prolonged QT syndrome or Torsades de Pointes.

Prior/Concomitant Therapy

7. Has received prior treatment with chemotherapy (**except** neoadjuvant/adjuvant chemotherapy), or with any CDK4/6 inhibitor.
8. Has received prior treatment with fulvestrant.
9. Use of systemic estrogens (eg, hormonal contraception, HRT).
10. Is currently receiving any of the following substances and cannot be discontinued 14 days prior to starting lerociclib:
 - Known strong or moderate CYP3A inducers or strong inhibitors of CYP3A

- Substances that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
11. Has evidence of active bacterial infection, fungal infection, or viral infection (including SARS-CoV-2 or uncontrolled HIV, as noted below) which would preclude safe enrollment in the judgment of the Investigator.
- **Notes:**
 - The study SARS-CoV-2 requirements are determined by institutional standards (and local/country regulations, as applicable).
 - At Investigator discretion, any participant who tests positive and/or is symptomatic for SARS-CoV-2 during Screening may either be excluded from the study or delay enrollment until active infection has been excluded per institutional standards.
 - During the study, any SARS-CoV-2 testing is to be performed as clinically indicated for the individual participant. The Investigator must document the results of all tests performed. Any confirmed infection is to be recorded as an AE or, in the event that clinical manifestation warrants such, recorded and handled as an SAE as detailed in [Appendix 3](#).

Diagnostic Assessments

12. Ejection fraction of $\leq 45\%$ on echocardiogram performed within the past 12 months, or documented history of congestive heart failure with reduced ejection fraction.
13. Oral temperature of $> 38^{\circ}\text{C}$ at Screening, or any evidence of SARS-CoV-2 infection.
14. Interstitial pneumonia or severe impairment of lung function, with the latter defined as having vital capacity AND DLCO that are $\leq 50\%$ of the normal predicted values OR having an O_2 saturation at rest in ambient environment of $\leq 88\%$.

5.3. Lifestyle Considerations

No restrictions are specified.

Based on current available data, lerociclib may be administered without regard to food; however, dosing under fed conditions appeared to improve gastrointestinal tolerability (Section [2.2.2.1](#)). For this reason, as well as for consistency across the study population, participants in this study will be advised to take lerociclib after eating.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information collected for this study will include informed consent date, demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failures) may be re-screened if their eligibility characteristics have changed.

If a participant fails to enroll during the 42-day Screening Period, a new participant number will be assigned at the time of re-screening, if applicable. Participants may not be entered into this study more than once.

5.4.1. Screening and Enrollment Log and Participant Identification Numbers

The participant's enrollment will be recorded in the Screening and Enrollment Log.

Upon enrollment (ie, at the time of signing the ICF), each participant will receive a unique participant identification number. This number is assigned by the IRT system. Participant numbers must not be re-used for different participants.

Each participant will be provided with a participant identification card on Day 1 of Cycle 1. This card will contain study site contact information to be used in the event of an emergency. Refer to Section 8 for details.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

All study participants will receive lerociclib (referred to herein as the IMP) every 28 days (± 2 days), and will also receive Investigator's choice of either letrozole or fulvestrant (referred to herein as NIMPs).

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 schedule for administration of goserelin for each individual participant is decoupled from the rest of the study visit schedule, and will be determined by the date of the participant's most recent dose of goserelin at the time of study entry (with "goserelin C1D1" defined as the date of the participant's most recent dose + 28 days, then every 28 days subsequently).

Details of the study interventions are provided in [Table 4](#).

Table 4: Study Intervention(s) Administered

| Intervention Label | Lerociclib | Letrozole | Fulvestrant | Goserelin |
|---------------------------------|--|--|---|--|
| Intervention Name | Lerociclib | Letrozole | Fulvestrant | ZOLADEX (goserelin acetate implant) – for pre- or perimenopausal female study participants and male participants |
| Intervention Description | Tablet taken orally, 50 mg or 150 mg, BID or as indicated in Section 6.5 | Tablet taken orally, 2.5 mg, QD | 500 mg, intramuscular injection, Q2W for initial 3 doses, then Q4W thereafter | Subcutaneous implant, 3.6 mg, Q4W |
| Type | Drug | Drug | Drug | Drug |
| Dosage Formulation | Tablet | Tablet | Solution | Implant |
| Unit Dose Strength(s) | 50 mg, 150 mg | 2.5 mg | 50 mg/mL | 3.6 mg |
| Dosage Level(s) | Starting dose: 150 mg BID or as indicated in Section 6.5 | 2.5 mg QD | Initial dose: 500 mg Q2W (Week 1 Day 1, Week 3 Day 1, Week 5 Day 1) Maintenance dose: 500 mg Q4W | 3.6 mg Q4W |
| Route of Administration | Oral | Oral | Intramuscular | Subcutaneous |
| Use | Experimental | Background intervention | Background intervention | Background intervention |
| IMP or NIMP | IMP | NIMP | NIMP | NIMP |
| Manufacturer | EQRx International, Inc. | STADApHarm GmbH and G Pharma Specialities Limited (ex-US) and Accord Healthcare (US) | EVER Neuro Pharma GmbH (ex-US) and Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd. (US) | AstraZeneca AB (ex-US) and TerSera Therapeutics (US) |
| Sourcing | Provided centrally by the Sponsor | Provided centrally by the Sponsor | Provided centrally by the Sponsor | Provided centrally by the Sponsor |

Table 4: Study Intervention(s) Administered (Continued)

| Intervention Label | Lerociclib | Letrozole | Fulvestrant | Goserelin |
|-------------------------------|--|--|---|---|
| Packaging and Labeling | Lerociclib will be provided in 60-cc bottles sealed with 33-mm child-resistant caps with 35 tablets per bottle. Each bottle will be labeled as required per country requirement. | Letrozole will be provided as 30-count blister pack (ex-US) or 30-count bottle (US) and will be labeled as required per country requirement. | Fulvestrant will be provided as 2 × 250 mg/5 mL syringe per carton and will be labeled as required per country requirement. | Goserelin (ZOLADEX) will be provided as a single 3.6-mg injection implant per carton and will be labeled as required per country requirement. |

BID = twice daily; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; Q2W = once every 2 weeks; Q4W = once every 4 weeks; QD = once daily; US = United States.

6.2. Preparation, Handling, Storage, and Accountability

Bottles of lerociclib tablets will be labeled and supplied to the pharmacist/designee, who will inventory the contents and document them according to the drug accountability requirements.

Dispensing instructions will be provided in the pharmacy manual and will be maintained in the pharmacy records.

All study interventions will be stored in a locked cabinet/secure area under applicable storage conditions at the site. Only the pharmacist/designee and designated personnel will have access to the IMP (lerociclib). Lerociclib tablets of all strengths are to be stored at the conditions specified in the EQ132-201 Pharmacy Manual.

The pharmacist/designee will verify the integrity of the clinical study supplies (storage conditions, correct amount received, condition of shipment, kit numbers, etc.) according to the Investigator site's SOPs.

At a minimum, the following data will be tracked on the drug accountability log at the site pharmacy:

- Date received
- Lot number
- Bottle number
- Date dispensed
- Participant number
- Identification of the person dispensing the drug
- Date returned

Records of study medication (used, lost, destroyed, and returned containers, individual bottles) should be made at each visit in the drug accountability and dispensing forms. Drug accountability and reconciliation will be checked and verified by the designated site staff during the study and by the site monitor during and at the completion of the study.

Once the site monitor has verified drug accountability at the site, any used drug remaining at the completion of the study will be destroyed. Unused and unopened study medication can be returned by the site monitor to the Sponsor at any point in the study. Please contact the Sponsor for further questions regarding drug accountability.

The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit and storage for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (eg, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

There are no specific measures to minimize bias as this is an open-label, single-arm study with no comparator. All participants will receive lerociclib.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention (NIMP or IMP) directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention (NIMP or IMP) and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

Note: Any participants whose compliance with any study intervention falls below 80% may potentially be discontinued from study treatment. Any such cases are to be discussed by the Investigator and Sponsor before a final decision is made. Refer to Section [7.2.1](#) for details.

A record of the quantity of all study interventions dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

6.5.1. Lerociclib

A participant may temporarily discontinue from study treatment with lerociclib for a duration of up to 14 days, for any reason. However, any such temporary discontinuations must be reported to the Medical Monitor. Refer to Section [7.1.2](#) for details.

This protocol allows some alteration from the currently outlined lerociclib dosing schedule, but the maximum daily dose will not exceed 300 mg. 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 NCI CTCAE v5.0.

No more than 2 lerociclib dose-level reductions in total are allowed for any participant. Toxicity that requires dose-level reduction more than twice will lead to permanent discontinuation of lerociclib dosing for the individual participant. No lerociclib dose re-escalations are allowed if the dose reduction was due to a lerociclib-related toxicity.

In cases where the relationship to lerociclib is unclear, the Investigator may re-challenge the participant after discussion with the Medical Monitor.

Dose reduction will only be performed if the symptom(s) is (are) related to lerociclib in the opinion of the Investigator and not related to the underlying disease. The dose level reductions below will be utilized for the purpose of lerociclib modifications for toxicities.

Table 5: Lerociclib Dose Modifications

| Dose Level | Lerociclib Dose |
|-----------------------|-----------------------|
| Starting dose | 150 mg BID |
| First dose reduction | 100 mg BID |
| Second dose reduction | 50 mg QAM, 100 mg QPM |

BID = twice daily; QAM = once every morning; QPM = once every evening.

An off-drug period of up to 14 days is permitted to allow recovery from any toxicity in order to meet the continuation criteria.

6.5.1.1. Dose Modifications for Hematologic Toxicity

Table 6: Lerociclib Dose Modifications for Hematologic Toxicity

| Grade of Hematologic Toxicity (per NCI CTCAE v5.0) ^a | Lerociclib Dose Adjustment |
|--|---|
| Grade 3 (any Grade 3 hematologic toxicity except those listed below) | Continue lerociclib and repeat CBC at next scheduled visit or within 7 days. No dose reduction required. Starting at Cycle 5 Day 1, participants with stable Grade 3 neutropenia may have the frequency of CBC monitoring reduced to a different frequency determined by Investigator, if approved by the Medical Monitor. |
| Grade ≥ 3 neutropenia (ANC ≥ 500 to $< 1000/\text{mm}^3$) associated with a documented infection or fever $\geq 38.5^\circ\text{C}$ or Grade ≥ 3 thrombocytopenia (platelets $< 50,000$ to $25,000/\text{mm}^3$) associated with bleeding | Withhold lerociclib and monitor counts weekly until ANC $\geq 1 \times 10^9/\text{L}$ OR platelet count $\geq 75 \times 10^9/\text{L}$ with no further bleeding. Resume therapy at the next lower dose. If no further dose reduction is possible (participant is already receiving the lowest dose), lerociclib treatment must be discontinued. |
| Grade 4 | Withhold lerociclib until the hematological toxicity has recovered to Grade ≤ 2 . Resume therapy at the next lower dose. If no further dose reduction is possible (participant is already receiving the lowest dose), lerociclib treatment must be discontinued. |

^a. Applies to all hematologic adverse reactions, except lymphopenia (unless associated with clinical events, eg, opportunistic infections).

ANC = absolute neutrophil count; CBC = complete blood count; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

The optimal treatment for IMP-induced neutropenia is to withhold lerociclib. Granulocyte colony-stimulating factor will not work in this setting because lerociclib induces a G₁ cell cycle arrest that cannot be overcome by G-CSF. Withholding lerociclib treatment will allow neutrophils to recover naturally.

Neutrophil counts should increase as the lerociclib concentrations in the body decline and the neutrophils are released from G₁ arrest.

If the participant experiences neutropenia lasting more than 10 days after the cessation of lerociclib, and the Investigator believes that G-CSF use is clinically indicated, then the Investigator must contact the Medical Monitor to discuss the use of G-CSF for that participant.

6.5.1.2. Dose Modifications for Non-hematologic Toxicity

For any non-hematologic toxicity of Grade ≥ 3 severity that persists despite optimal medical treatment, withhold treatment with lerociclib until symptoms resolve to Grade ≤ 2 severity (if not considered a safety risk for the participant). If the treatment interruption duration is > 14 days, approval from the Medical Monitor will be needed to resume treatment.

Treatment should be resumed at the next-lower dose level of lerociclib. If no further dose reduction is possible (participant is already receiving the lowest dose), lerociclib treatment must be discontinued.

6.5.2. Letrozole, Fulvestrant, and Goserelin

Dose modification of letrozole, fulvestrant, or goserelin is not allowed during the study for any participant.

6.6. Missed Doses

In the event that a participant misses a dose of lerociclib, that participant should resume lerociclib at the next scheduled dose. No attempts should be made to make up for missed doses.

6.7. Continued Access to Lerociclib after the End of the Study

Participants who have completed all scheduled clinical study visits and continue to show benefit from lerociclib will be eligible to participate in a rollover study for continued access to lerociclib.

6.8. Definition and Treatment of Overdose

Note: “Overdose” and “noncompliance” are not interchangeable in this protocol. This section refers specifically to overdose in the context of a clinical study. Refer to Section 6.4 for information regarding study intervention compliance.

In the context of a clinical study, an overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol.

In this study, if an overdose on any study intervention, including the IMP (lerociclib), occurs in the course of the study, then the Investigator or other site personnel shall inform the appropriate Sponsor representatives immediately, or no later than 24 hours of first becoming aware of it. The designated Sponsor representative shall work with the Investigator to ensure that all relevant information is provided to the Sponsor or designee.

For overdoses associated with an AE/SAE, the standard reporting timelines apply.

There is no specific treatment in the event of lerociclib overdose, and symptoms of overdose are not established. In the event of an overdose, the Investigator should hold lerociclib, follow general supportive measures, and treat symptomatically.

6.9. Prior and Concomitant Therapy or Procedures

The Investigator or qualified designee will review prior medication use, including prescription medications, over-the-counter preparations, growth factors, blood products, and parenteral nutrition, and record prior medications taken by the participant within 14 days prior to the first day of Screening Visit.

The Investigator or qualified designee will record medication, if any, taken by the participant during the study through the last study visit.

Documentation will include information regarding start and stop dates, dose(s), and reasons for the medication use.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Administration of other concomitant, non-protocol, anticancer therapies prior to disease progression is not permitted while receiving IMP (lerociclib) during the study (not including EOT/ED, Safety Follow-up, and long-term Survival Follow-up).

Administration of other concomitant investigational agents for any indication is not permitted while receiving IMP (lerociclib) during the study (not including long-term Survival Follow-up).

Granulocyte colony-stimulating factor may not be used during the first 4 weeks on study. After the first 4 weeks on study, the Investigator must contact the Medical Monitor if they believe that G-CSF use is clinically indicated for a study participant that has temporarily stopped lerociclib and is experiencing prolonged neutropenia (more than 10 days after the cessation of lerociclib).

Use of a 5-HT₃ antagonist may be used on an as needed basis but should be used with caution at the Investigator's discretion. Symptomatic management of diarrhea with loperamide, when required, should commence in a timely fashion. Sites should ensure that participants are adequately informed on the proper use of loperamide.

CYP3A4 Substrates

Lerociclib has the potential to inhibit CYP3A4/5 in both a competitive and time-dependent manner based on in vitro studies.

Using the FDA-recommended model-based predictions in the guidance for drug interaction studies ([FDA 2020](#)), lerociclib has the potential to significantly inhibit CYP3A4 in the gut and thus may have a clinically significant effect on orally administered CYP3A4 substrates with a narrow therapeutic index, and such drugs are prohibited during participation in this study (beginning 14 days prior to the first dose of lerociclib, until 14 days after the last dose of lerociclib).

- Prohibited, orally administered CYP3A substrates with a narrow therapeutic index:
 - astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, everolimus, pimozone, quinidine, sirolimus, and tacrolimus

- **Monitor frequently for adverse reactions** with concomitant use of drugs that are orally administered CYP3A substrate drugs, with consideration of dose reduction of the substrate if clinical signs and symptoms of toxicity emerge (eg, muscle aches with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors).

The model-based calculation for inhibition of CYP3A4 in the liver predicts a marginal inhibitory effect by lerociclib and therefore the likelihood of a clinically significant drug interaction for CYP3A substrates administered via routes other than oral (eg, IV, transdermal, inhalation, etc) is low.

- **Caution should be exercised** with concurrent use of non-orally administered CYP3A substrates with a narrow therapeutic index with consideration of dose reduction of the substrate if clinical signs and symptoms of toxicity emerge (eg, increased somnolence with transdermal fentanyl or IV midazolam).

CYP3A4 Inhibitors and Inducers

Lerociclib is a substrate for CYP3A4, although the extent of metabolism by CYP3A4 is expected to be low in humans since the in vitro clearance of lerociclib in human liver microsomes and hepatocytes was low. Lerociclib exposure may be altered by concomitant use of drugs that are strong CYP3A inhibitors or inducers. Concomitant use of drugs that are strong or moderate CYP3A inducers is to be avoided.

- Prohibited drugs that are strong or moderate CYP3A inducers include the following:
 - phenytoin, rifampin, carbamazepine, St John's Wort, bosentan, modafinil, and nafcillin
- **Monitor frequently for adverse reactions** with concomitant use of drugs that are strong CYP3A inhibitors (eg, grapefruit juice, aprepitant, clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, verapamil, and voriconazole).

CYP2C8 Inhibitors and Inducers

Lerociclib is a substrate for CYP2C8, although the extent of metabolism by CYP2C8 is expected to be low in humans since the in vitro clearance of lerociclib in human liver microsomes and hepatocytes was low. Lerociclib exposure may be altered by concomitant use of drugs that are strong CYP2C8 inhibitors or inducers.

- **Caution should be exercised** with concomitant use of drugs that are strong inhibitors of CYP2C8 (eg, gemfibrozil, quercetin, sulfapyrazone, trimethoprim, and nicardipine).
- **Monitor for efficacy** with concomitant use of drugs that are strong or moderate inducers of CYP2C8 (eg, rifampin, phenobarbital, and carbamazepine).

Bisphosphonates and Denosumab

Bisphosphonates and denosumab for the treatment of osteoporosis or management of existing bone metastases may be continued for participants who have been receiving them at a stable dose for at least 14 days prior to first dose of lerociclib.

However, the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of participant from the study unless disease progression can be completely ruled out and the exact reason for the use of these therapies is clearly documented in the participant's source documentation. Such cases must be discussed with the Medical Monitor first.

Medications Not Recommended

Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or by inhalation, as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.

Any use of systemic corticosteroids for reasons other than those mentioned above shall be discussed with the Medical Monitor prior to use.

The use of herbal medicine is not recommended.

Additional Cautions

Lerociclib inhibited P-gp, BCRP, MATE1, MATE2-K, and OCT1 and OCT2 membrane transporters and therefore caution should be exercised with concomitant use of drugs that are substrates for these transporters. MATE2-K is involved with tubular secretion of creatinine and inhibition of MATE2-K by lerociclib may cause an increase in serum creatinine levels unrelated to true changes in renal function.

Lerociclib is a substrate and inhibitor of P-gp and BCRP efflux transporters. Lerociclib exposure may be altered by concomitant use of drugs that are strong inhibitors or inducers of P-gp or BCRP.

- Monitor for adverse reactions when co-administering medications that are strong inhibitors of P-gp and BCRP.

Concomitant Radiotherapy and Surgery

Palliative radiotherapy may be permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the Investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression.

Approval from the Medical Monitor should be obtained prior to any surgery or start of alternative therapy that are not considered palliative.

Any diagnostic, therapeutic, or surgical procedures performed while the participant is receiving IMP (lerociclib) during the study period will be documented. Documentation will include information regarding the date(s), indication(s), description of the procedure(s), and any clinical or pathological findings.

Medications will be coded using the WHO Drug Dictionary.

7. DISCONTINUATION FROM STUDY TREATMENT AND FROM THE OVERALL STUDY

Discontinuation of specific study sites is handled as part of the appendix on governance (Section 10.1.9).

Refer to Section 7.4 for criteria that may potentially result in permanent stoppage (discontinuation) of the overall clinical study.

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation of a Participant from Study Treatment

It may be necessary for a participant to permanently discontinue from study treatment. If a participant is permanently discontinued from study treatment, that participant will remain in the study to be evaluated for safety follow-up, including survival follow-up. See the SoA (Table 1) for data to be collected at the time of the participant's discontinuation from study treatment and at follow-up, and for any further evaluations that will need to be completed.

A participant's treatment with the IMP (lerociclib) will be permanently discontinued if any of the following events occurs during the study:

- The participant suffers an AE that, in the judgment of the Investigator, Sponsor, or Medical Monitor, presents an unacceptable risk to the participant.
- General or specific changes in the participant's condition (eg, a significant intercurrent illness or complication) that, in the judgment of the Investigator, are unacceptable for further administration of study intervention.
- Change in the participant's compliance with any inclusion/exclusion criterion that is clinically relevant and affects participant safety as determined by the Investigator (or designee).
- Noncompliance with the study restrictions that might affect the participant's safety or the study assessments/objectives, as considered applicable by the Investigator (or designee).
- The participant has any of the following:
 - Serum ALT or AST $> 3 \times$ ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain, or tenderness, fever, rash, and/or eosinophilia (eosinophil % is $> 5\%$ [eosinophil % = absolute eosinophil count/total white blood cells])
 - Alanine aminotransferase or AST $> 5 \times$ ULN
 - Alanine aminotransferase or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN ($> 35\%$ direct bilirubin), OR ALT or AST $\geq 3 \times$ ULN and INR > 1.5 (if INR measured)
- Occurrence of pregnancy in a female study participant or female partner of a male study participant (as applicable).
- Significant noncompliance of the participant with protocol requirements

Note: This includes any participant whose compliance with any study intervention falls below 80%. In such cases, potential discontinuation of the participant from study treatment will be discussed between the Investigator and Sponsor before a final decision is made.

- The Sponsor or legal representative of the Sponsor requests the participant to withdraw.
- The participant has documented disease progression.
- The participant is lost to follow-up.
- The participant exhibits any evidence of drug abuse.
- Permanent study treatment discontinuation is judged by the Investigator to be in the best interest of the participant.
- The participant withdraws consent.
- The Sponsor makes the decision to terminate the site or study.

In the event of a participant discontinuing from IMP (lerociclib) treatment (without withdrawal of consent from the study), that participant should be strongly encouraged to complete all protocol-scheduled assessments—to include the Safety Follow-up Visit 30 days after the last dose of lerociclib and the Post-Treatment Follow-up Phase (which includes a Survival Follow-up Phase that is to continue until at least 50% of enrolled participants have died).

A participant who discontinues from study treatment for reasons other than PD will have a CT or MRI scan performed during the Post-Treatment Visit if that participant has not had a scan performed within the prior 4 weeks.

The Investigator will document the reason for each participant's discontinuation from lerociclib treatment on the applicable eCRF page. When a participant's discontinuation from lerociclib is due to either an SAE or a Grade 3 or 4 toxicity considered to be related to the IMP, the Investigator should follow the event until resolution, stabilization, or it is deemed that further recovery is unlikely. Data on these events should be collected on the AE form in the eCRF.

In the event that a participant discontinues from lerociclib due to an AE or pregnancy, the Investigator should notify the Sponsor Medical Monitor or Pharmacovigilance representative by email within 24 hours of IMP discontinuation.

7.1.2. Temporary Discontinuation of a Participant from Study Treatment

A participant may temporarily discontinue from study treatment for a duration of up to 14 days, for any reason. However, any such temporary discontinuations must be reported to the Medical Monitor and study assessments must continue as specified in the SoA.

If the IMP (lerociclib) is temporarily discontinued for any study participant, it may be restarted within the aforementioned 14-day period under the discretion of the Investigator with notice to the Medical Monitor. Beyond a duration of 14 days, the participant may not re-start lerociclib therapy and will be removed from the study.

7.1.3. Re-challenge Therapy

Participants may re-challenge therapy for any reason, including toxicity, according to prespecified criteria and with the explicit permission of the Medical Monitor.

If therapy has been stopped due to toxicity, the Investigator must confirm the toxicity is resolving (to at least Grade 2 or better severity) before attempting re-challenge.

If therapy has been discontinued for any other reason, that reason must be provided to the Medical Monitor.

7.2. Permanent Discontinuation/Withdrawal of a Participant from the Study

A participant may permanently discontinue/withdraw from the study at any time at their own request, or may be permanently discontinued/withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. Any such participant will be permanently discontinued from the study interventions and the overall study at that time. If a participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent, subject to any limitations under applicable data privacy and data protection laws.

If a participant permanently discontinues/withdraws from the study, that participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records and notify the Sponsor.

If a participant permanently discontinues/withdraws from the study during the Treatment Phase, if possible, an ED Visit should be conducted, as shown in the SoA ([Table 1](#)). Refer to the SoA for details of the data to be collected at the time of study discontinuation and follow-up, and for any further evaluations that need to be completed.

If a participant permanently discontinues/withdraws from the study during the Post-Treatment Follow-up Phase prior to death, that participant will be censored from the OS analysis.

7.2.1. Criteria for Permanent Participant Discontinuation/Withdrawal from the Study

All participants should be encouraged to complete all study evaluations. However, participants may withdraw consent to participate in this study at any time without penalty or loss of benefits to which they are otherwise entitled.

Every reasonable effort should be made to determine the reason a participant withdraws consent to participate in this study; this information should be recorded on the appropriate page(s) of the eCRF. Where participants discontinue study intervention prematurely without withdrawing consent, reasonable efforts should be made to obtain all protocol-specified assessments to avoid losing outcome data needed to evaluate safety.

Participants may withdraw from the study at their own discretion (or at the discretion of the Investigator) for any reason at any time. The list of reasons for withdrawing participants from the study may include, but is not limited to, the following:

- Occurrence of an AE that, in the opinion of the Investigator, warrants the participant's permanent withdrawal from treatment.
 - In the event of IMP (lerociclib) withdrawal due to the occurrence of a nonserious AE, the study site should notify the Sponsor or Sponsor's representative as soon as possible.

- In the event of study intervention withdrawal due to the occurrence of an SAE, the Medical Monitor or representative must be notified within 24 hours.
- Participants withdrawn secondary to an ongoing, nonserious AE, regardless of causality, or an SAE that is not related to IMP (lerociclib) must be followed clinically until 14 days after the last dose of IMP was administered.
- Participants withdrawn secondary to an ongoing SAE that is considered related to IMP (lerociclib) must be followed clinically until resolution or stabilization.
- Significant noncompliance, defined as refusal or inability to adhere to the prescribed dosing and follow-up regimen

Note: As described previously, for any participant whose compliance with any study intervention falls below 80%, potential discontinuation from study treatment is to be discussed between the Investigator and Sponsor before a final decision is made.

- Request of the participant, Investigator, or study Sponsor
- Withdrawal of informed consent
- Lost to follow-up (must have at least 2 documented attempts to contact the participant)
- Death

All data and lab samples collected prior to the date of withdrawal of consent will remain in the clinical database and at the laboratory vendor.

7.2.2. Replacement of Study Participants

Participants who do not ever receive the IMP (lerociclib) will be replaced. Any replacement participant will receive a new participant number.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if that participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined), counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods) and regain any remaining IMP from the participant. The Investigator should be making every effort to collect any unused medication. These contact attempts should be documented in the participant's medical record/eCRF.

- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

A participant will be considered lost to follow-up after 3 months of documented contact attempts.

7.4. Criteria for Potential Stoppage (Permanent Discontinuation) of the Study

The Sponsor will review the evaluable data, including any emerging safety signals attributed to study drug, and will consider whether the permanent stoppage (discontinuation) of the study may potentially be appropriate. Additional details will be provided in the DSMB Charter document, as described in Section [10.1.5.1](#).

As noted in Section [4.4](#), stoppage (permanent discontinuation) of the study may also occur in any of the following circumstances:

- Overall, country-/region-specific, or site-specific stoppage by the Sponsor at any time, for any reason
- Stoppage in a specific country or region by the relevant Health Authority
- Stoppage at a specific site by the relevant IRB/IEC or by the Principal Investigator (refer to the relevant portion of the appendix on governance [[Section 10.1.9.3](#)])

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA ([Table 1](#)). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be used for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed approximately 300 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Participant Identification Card

On Day 1 of Cycle 1, all participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The Investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent.

Medical History

A medical history will be obtained by the Investigator or qualified designee. The medical history will collect all medical and surgical conditions that the Investigator considers to be clinically significant and relevant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

Calibration of Equipment

The Investigator (or qualified designee) is responsible for ensuring that any device or instrument used for a clinical evaluation/test during the study that provides information about eligibility criteria and/or safety or efficacy parameters is suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Equipment calibration documentation is to be retained at the study site and available for inspection.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA ([Table 1](#)).

8.1.1. Antitumor Activity Assessments

For tumor assessment, all sites of disease, including but not limited to the chest, abdomen, and pelvis, should be assessed radiologically by CT or MRI at Screening and every 8 weeks for the first 12 months, then every 12 weeks until the occurrence of disease progression ([Table 1](#)). A central imaging vendor will be used to collect and hold these images for possible future review by independent radiologists. Objective response data collected for the clinical study report will be based on Investigator assessment.

Scans (CT or MRI) obtained prior to informed consent will not need to be repeated if performed within 28 days prior to dosing. Radionuclide bone scans shall be performed at Screening for all participants and annually thereafter or as clinically indicated. All participants with a CR must have a radionuclide bone scan as part of confirmation of the CR. Additional scans may be obtained at the discretion of the Investigator, if clinically indicated.

Participants with bone-only disease will be followed with bone scans only at Screening and every 12 weeks on treatment.

If a participant shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. Participants who have a confirmed CR will have a bone scan to confirm absence of bony metastases.

For all participants (1L or 2L populations), if they remain on therapy for 12 months following enrollment, the timing of CT or MRI scans should be lengthened to every 12 weeks.

The same method of assessment (CT or MRI) should be used to characterize tumors at Screening and at all follow-up assessments. If PET is used, it should also be accompanied by spiral CT or MRI.

Investigators should follow RECIST v1.1 Guidelines ([Eisenhauer 2009](#)) for tumor assessments and determination of overall response.

8.1.1.1. Lesions: Identification and Follow-up

Measurable Lesions

Measurable tumor lesions are defined as tumor lesions with an LD (measured in at least 1 dimension) with a minimum size as follows ([Eisenhauer 2009](#)):

- 10 mm by CT or MRI (with a scan slice thickness of no greater than 5 mm)

Measurable lymph nodes must be ≥ 15 mm on the short axis by CT or MRI (with a scan slice thickness of no greater than 5 mm); only the short axis is to be measured at baseline and follow-up.

Lytic bone lesions or mixed lytic-blastic lesions with a soft tissue component meeting the definition of measurability above can be considered measurable lesions.

Cystic lesions representing cystic metastases that meet the definition of measurability described above can be considered measurable lesions. If present, noncystic lesions should be selected as target lesions for this study.

A tumor lesion that has been previously irradiated may be considered measurable if unequivocal growth of the lesion has been demonstrated.

Target lesions: At baseline, up to 5 measurable tumor lesions/lymph nodes (with a maximum of 2 lesions per organ) should be identified as target lesions that will be followed to quantitate the status of disease during the study. Lesions with the LD, that are representative of all involved organs, and for which reproducible repeated measurements can be obtained should be selected as the target lesions.

At Screening and at each follow-up timepoint ([Table 1](#)), each target lesion should be measured and the overall tumor burden will be calculated as the sum of the diameters of the target lesions (LD for tumor lesions and short axis for lymph nodes) and documented in the eCRF. If a target lesion fragments into multiple smaller lesions, the LDs of all fragmented portions are added to the sum of the diameters. If multiple lesions coalesce, the LD of the coalesced lesion will be included in the sum of the diameters.

Nonmeasurable Lesions

Nonmeasurable lesions include tumor lesions with an LD < 10 mm, lymph nodes with ≥ 10 to < 15 mm short axis, or nonmeasurable lesions such as leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by CT scan or MRI ([Eisenhauer 2009](#)).

Nontarget lesions: All other lesions (or sites of disease) identified at baseline should be identified as nontarget lesions and recorded in the eCRF. Measurements of these lesions are not required, but the presence, absence, or unequivocal progression of each nontarget lesion should be recorded in the eCRF at each follow-up timepoint. Multiple nontarget lesions in the same organ may be noted as a single item on the eCRF.

New Lesions

Any new lesions should be identified and recorded at each follow-up assessment, as these are markers of disease progression. As defined in the RECIST v1.1 Guidelines ([Eisenhauer 2009](#)), new lesions include the following:

- A lesion in an anatomical location that was not scanned at baseline
- Equivocal new lesion of small size that with continued therapy and follow-up is found to progress and represent new disease (progression should be considered as of the date of the initial scan)
- Negative PET with FDG-PET at baseline, but has a positive FDG-PET at follow-up

No FDG-PET at baseline and a positive FDG-PET at follow-up that corresponds to a new site of disease as confirmed by CT (date of disease progression should be the date of the initial abnormal FDG-PET scan).

The need to initiate or increase the dose of a bisphosphonate and/or denosumab during the study **will be considered as indicative of clinical disease progression** leading to the discontinuation of participant from the active treatment phase **unless** disease progression can be completely ruled out and the exact reason for the use of these therapies is clearly documented in the participant's source documentation. All such cases must be first discussed with the Medical Monitor.

Note: Findings attributable to differences in scanning technique or a change in type of imaging (CT versus MRI) and findings representing something other than tumor (eg, healing or flare of existing bone lesions, necrosis of a liver lesion) should not be considered new lesions.

8.1.1.2. Definitions of Tumor Response and Disease Progression

The determination of tumor response and progression will be based on the RECIST v1.1 criteria ([Eisenhauer 2009](#)). The definitions for tumor response per RECIST, v1.1 are provided below.

Evaluation of Target Lesion Response

- **Complete response:** Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm
- **Partial response:** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progression of disease:** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression
- **Stable disease:** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study

A response category of not evaluable is to be used when there is inadequate information to otherwise categorize the response status.

Evaluation of Nontarget Lesions

- **Complete response:** Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be < 10 mm short axis
- **Non-CR/Non-PD:** Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits
- **Progression of Disease:** Unequivocal progression of existing nontarget lesions or the appearance of at least 1 new lesion

Evaluation of Overall Response

[Table 7](#) describes the evaluation of overall response at each timepoint based on target and nontarget lesion responses at each timepoint, as well as the appearance of new lesions. The best overall response is the best response recorded from the start of the treatment until disease progression. Confirmation of CR and PR is required as previously described.

Table 7: Evaluation of Overall Response at Each Timepoint

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response |
|----------------|-------------------|-------------|------------------|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Not evaluated | No | PR |

Table 7: Evaluation of Overall Response at Each Timepoint (Continued)

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response |
|----------------|--------------------------|-------------|------------------|
| PR | Non-PD/not all evaluated | No | PR |
| SD | Non-PD/not all evaluated | No | SD |
| NE | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
Source: [Eisenhauer 2009](#)

8.1.2. Patient-reported Outcomes

Patient-reported outcomes will be assessed in all participants as indicated in the SoA ([Table 1](#)) using the following PRO measures: the EORTC questionnaire developed to assess the QoL of cancer patients (EORTC-QLQ-C30), the EORTC questionnaire for assessing QoL in breast cancer patients (EORTC-QLQ-BR23), the EQ-5D-5L questionnaire, and the FACIT item GP 5 (“I am bothered by side effects of treatment”) rated on a 5-point Likert scale. Please refer to [Appendix 5](#) for samples of these 4 questionnaires.

Questionnaires and instructions will be provided electronically.

When possible, the questionnaires are to be completed in the same order at each visit and should be completed before any other procedures are performed.

If the participant is unable to complete the questionnaire during one of the scheduled visits, then the reason for not completing the questionnaire should be documented.

8.2. Safety Assessments

Safety evaluations will be conducted at Screening and throughout the study. Safety evaluations will include monitoring of AEs, vital signs measurements, physical examinations, 12-lead ECGs, and clinical laboratory assessments.

Planned timepoints for all safety assessments are provided in the SoA ([Table 1](#)).

The toxicity of lerociclib administered with either letrozole or fulvestrant will be assessed by Investigator s using the NCI CTCAE v5.0.

8.2.1. Physical Examinations

Physical examinations will be performed at the timepoints outlined in the SoA ([Table 1](#)).

8.2.1.1. Physical Examination

Full physical examination evaluations at Screening should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations.

A physical examination must be performed on Day 1 of every cycle. According to the Investigator's judgement, this can be an abbreviated physical examination (ie, symptom-directed to include body systems as appropriate).

Information about the physical examination must be present in the source documentation at the study site. Clinically significant findings on physical examinations conducted after consent must be reported according to the AE/SAE reporting guidance in [Appendix 3](#).

Clinically significant findings on physical examinations conducted after the first dose of any study intervention that meet the definition of an AE or SAE (refer to [Appendix 3](#)) must be recorded as an AE/SAE.

8.2.1.2. Body Weight and Height

Body weight (in kg) will be measured by site staff under the following conditions: participant in light clothing and without shoes after having emptied his/her bladder.

The participant's height (in cm) will be measured (without shoes) at Screening only to calculate the body mass index.

8.2.1.3. Eastern Cooperative Oncology Group Performance Status

The assessment of ECOG PS will be performed following the grading described in [Table 8](#).

Table 8: Eastern Cooperative Oncology Group Performance Status

| PS | ECOG |
|----|--|
| 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, eg, light housework, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair |
| 5 | Dead |

ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Source: [Oken 1982](#)

8.2.2. Vital Signs

Vital signs will be assessed at the timepoints as outlined in the SoA ([Table 1](#)).

Vital signs (to be taken before blood collection for laboratory tests) will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

Body temperature will be measured using the same method according to local practice. The measured values are to be recorded in degrees Celsius.

Respiratory rate will be measured by counting breaths over a period of 1 minute (breaths/min) after a resting period of at least 5 minutes in semi-supine/supine position.

8.2.3. Electrocardiograms

All 12-lead ECGs will be obtained as outlined in the SoA ([Table 1](#)), using an ECG machine that automatically calculates the heart rate and measures P-R, QRS, QT, QTcB, and QTcF intervals. The same make and model ECG machine should be used within each participant. Participants should rest in a semi-supine/supine position for at least 5 minutes prior to each ECG assessment.

At each timepoint at which triplicate 12-lead ECG recordings are required per the SoA, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

The Investigator or qualified designee should review the ECGs for any abnormalities as compared with predose ECGs.

A central ECG vendor will be used to collect and hold the ECGs in the event that the Sponsor has any questions related to the results. The ECG safety data collected for the clinical study report will be based on Investigator assessment.

8.2.4. Clinical Safety Laboratory Tests

Refer to [Appendix 2](#) for the list of clinical laboratory tests to be performed and to the SoA ([Table 1](#)) for the timing and frequency of these tests.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Note: All events of ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN ($> 35\%$ direct bilirubin) OR ALT or AST $\geq 3 \times$ ULN and INR > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's Law), **must be reported to the Sponsor in an expedited manner (within 24 hours of awareness).**

Abnormal laboratory findings associated with the participant's underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

Clinically significant findings on laboratory assessments conducted after consent must be reported according to the AE/SAE reporting guidance in [Appendix 3](#).

Clinically significant findings on laboratory assessments conducted after the first dose of any study intervention that meet the definition of an AE (refer to [Appendix 3](#)) must be recorded as an AE.

All laboratory tests with values considered abnormal and clinically significant during participation in the study or within 30 days after the last dose of any 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.

- If any values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, where possible, and the Sponsor notified.

- All protocol-required laboratory tests, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory manual and the SoA ([Table 1](#)).
- If laboratory values from laboratory tests not specified in the protocol and performed at the institution's local laboratory result in the need for a change in participant management or are considered clinically relevant by the Investigator (eg, are considered to be an SAE or an AE or require dose modification), then the results must be recorded.

Blood and urine samples will be collected for clinical laboratory assessments as outlined in the SoA ([Table 1](#)).

8.2.5. Pregnancy Testing

For any female participant who is of childbearing potential (as defined in [Appendix 4](#)), serum β -hCG pregnancy testing will be performed at Screening. Serum or urine β -hCG pregnancy testing will be performed at Day 1 of each cycle before the administration of lerociclib. Pregnancy test(s) may be performed at the discretion of the Investigator at any other time during the study.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in [Appendix 3](#). Treatment-emergent AEs are defined as AEs starting at or after the first dose of any study intervention (NIMP or IMP). Additional details will be provided in the study SAP.

All AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or a legally authorized representative).

All AEs (including SAEs) occurring during the study will be reported in the eCRF. This includes all events from the time following Screening, up to and including the Post-Treatment Follow-up Phase, whether or not attributed to the IMP (lerociclib) and observed by the Investigator or the participant. Any ongoing SAEs should be followed up until resolution wherever possible.

All SAEs occurring during the study must be reported via email to BOTH the Sponsor and CRO using the Severe or Serious Adverse report form with any other supporting information per the process outlined in [Appendix 3](#) and recorded in the AE section of the eCRF. Any ongoing SAEs should be followed up until resolution wherever possible.

For deaths, the working diagnosis or cause of death as stated on a death certificate, available autopsy reports, and relevant medical reports should be sent to both EQRx International, Inc. and the Parexel Pharmacovigilance Group promptly.

Definite progression of disease under study, including signs and symptoms of progression assessed by the Investigator, should not be reported as an AE or SAE.

Death unequivocally due to disease progression, as agreed by both the Investigator and the Sponsor Medical Monitor, should be documented in the eCRF but not be reported as an SAE.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up until resolution wherever possible ([Appendix 3](#)).

The methods of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Appendix 3](#).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the time of obtaining informed consent through the Post-Treatment Follow-up Phase, as detailed above in Section [8.3](#). All SAEs will be recorded using the Serious Adverse Event report form with any other supporting information, and recorded in the AE section of the eCRF and reported via email to BOTH the Sponsor and CRO within 24 hours of awareness, as indicated in [Appendix 3](#). The Investigator will submit any updated SAE data, as described in [Appendix 3](#), within 24 hours of discovery or notification of the event.

Investigators are not obliged to actively seek information on AEs or SAEs past 30 days after the last dose of any study intervention (NIMP or IMP). However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Adverse events may also be detected upon physical examination.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section [7.3](#)). Further information on follow-up procedures is given in [Appendix 3](#).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification (within 24 hours; see [Appendix 3](#)) by the Investigator to BOTH EQRx International, Inc. and the Parexel Pharmacovigilance Group of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC.

All SAEs that occur during the study, and all SAEs occurring up to 30 days after receiving the last dose of any study intervention (NIMP or IMP), whether considered to be associated with the study intervention or not, must be reported within 24 hours to BOTH EQRx International, Inc. and the Parexel Pharmacovigilance Group using the email addresses in the List of Study Personnel.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5. Pregnancy

Details of all pregnancies in female study participants and female partners of male study participants (as applicable) will be collected after the start of any study intervention (NIMP or IMP) and until at least 365 days (1 year) after the last dose of study intervention.

If a pregnancy is reported, the Investigator will record pregnancy information on the Pregnancy form and submit it to the Sponsor within 24 hours of learning of the pregnancy of a female study participant or female partner of a male study participant (as applicable). The Investigator should then follow the procedures outlined in [Appendix 4](#).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs and will be reported as such.

All pregnant female study participants and pregnant female partners of male study participants (as applicable) will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the mother of the neonate and the neonate 90 days after the delivery, and the information will be forwarded to both EQRx International, Inc. and the Parexel Pharmacovigilance Group.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to both EQRx International, Inc. and the Parexel Pharmacovigilance Group as described in [Appendix 3](#). The Investigator is not obligated to actively seek this information in former study participants, but may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and will be withdrawn from the study. In the event of such a withdrawal by a pregnant participant, the Investigator should make every effort to follow the participant until the completion of the pregnancy.

The Investigator should also make every effort to follow until completion any pregnancy occurring in the female partner of a male study participant, as applicable.

8.4. Pharmacokinetics

Blood samples of approximately 60 mL will be collected for measurement of plasma concentrations of lerociclib at the visits as specified in the SoA ([Table 1](#)). The actual date and time of each sample collection will be recorded in the source documents and in the eCRF.

Details on sample collection, processing, and shipment will be provided in the laboratory manual. All samples will be analyzed by the designed analytical laboratory using a validated bioanalytical method in compliance with regulatory requirements.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

The study SAP will be finalized prior to the database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

No formal statistical hypothesis will be tested; the analysis will be descriptive in nature.

9.2. 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 (NIMP or IMP).
- Full Analysis Set is defined as all enrolled participants who were exposed to lerociclib during the study.
- Response Evaluable 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. Tumor response endpoints will be assessed using the Response Evaluable Analysis Set. Progression-free survival, OS, and QoL will be assessed using the FAS.

9.3. Statistical Analyses

Full details on the statistical analyses to be performed will be provided in a separate SAP.

9.3.1. General Considerations

Descriptive summaries for categorical variables will include counts and percentages. Descriptive summaries for continuous variables will include means, medians, standard deviations, and minimum and maximum values. Descriptive summaries of time-to-event data will include median, 25th and 75th percentiles, and 95% CIs (where applicable) based on Kaplan-Meier methods. All analyses will be performed by line of therapy.

9.3.2. Primary Endpoint(s) Analysis

The primary analysis will occur approximately 6 months after the last participant receives the first dose.

9.3.2.1. Analysis of Adverse Events

Adverse event data will be coded by SOC and PT using the current version of the MedDRA. The number and percentage of participants experiencing any TEAE and serious TEAE, overall, and by SOC and PT will be tabulated. Treatment-emergent AEs will also be summarized by severity grade (as assessed by the Investigator per NCI CTCAE v5.0).

Treatment-emergent AEs and SAEs related to treatment (ie, study intervention) will be further summarized by the treatment to which each is attributed (eg, lerociclib, letrozole, fulvestrant, or goserelin). Withdrawals due to AEs will be summarized.

Duration of AEs will be determined and included in the listings, along with action taken and outcome. Adverse events leading to treatment discontinuation will also be listed.

9.3.3. Secondary Endpoint(s) Analysis

9.3.3.1. Other Safety Endpoints

Observed values and changes from baseline in vital signs, 12-lead ECG readings, and clinical laboratory parameters will be tabulated at each visit; by visit summaries will be based on scheduled, nominal visits.

Toxicities for clinical laboratory parameters will be characterized according to NCI CTCAE v5.0. Shifts in NCI CTCAE toxicity grades will be summarized. Vital signs and clinically significant findings on physical examination will be listed by participant.

Dose reductions/modifications, interruptions, compliance, and participant exposure will be summarized for each study therapy component, where appropriate.

9.3.3.2. Assessment of Tumor Response and Clinical Benefit

The ORR is defined as the percentage of participants achieving a confirmed CR or confirmed PR based on RECIST v1.1.

The CBR is defined as the percentage of participants having achieved a confirmed CR, confirmed PR, or SD (for at least 8 weeks).

Objective response rate and CBR will be summarized along with the associated 2-sided exact 95% CIs based on the Clopper-Pearson method.

9.3.3.3. Progression-free Survival and Overall Survival

Progression-free survival is measured from the date of the first dose of lerociclib in Cycle 1 until the date of the first documented disease progression or death. Diagnosis of PD will be based on RECIST v1.1; censoring methods for participants who do not experience PD or death will be described in the study SAP.

Overall survival is measured from the date of first dose of lerociclib until death. Censoring methods for participants who do not experience fatalities during the course of the study will be identified in the study SAP.

Descriptive summaries of time to event data will include median, 25th and 75th percentiles, and associated 2-sided 95% CIs based on Kaplan-Meier methods. Survival distribution function estimates along with corresponding 95% CIs using the log-log transformation will be provided at 6-month intervals as data allows. Kaplan-Meier plots of the survival distribution function will be presented and will include the number of participants at risk over time. No formal statistical hypothesis will be tested.

9.3.3.4. Duration of Response

For participants with confirmed CR or PR, the DOR is defined as the time from the date of the first documentation of response until the date of the first documented disease progression or death.

Diagnosis of PD will be based on RECIST v1.1; censoring methods for participants who do not experience PD or death will be described in the study SAP. Time to event analysis methods, as described for PFS and OS will be used for the analysis of this endpoint.

9.3.3.5. Time to Response

For participants with confirmed CR or PR, the TTR is defined as the time from the date of the first dose of lerociclib until the first documented response (CR or PR). Diagnosis of CR or PR will be based on RECIST v1.1.

9.3.3.6. Patient-reported Outcomes

The EORTC-QLQ-C30, the EQ-5D-5L, and the FACIT item GP5 will be summarized at baseline and on Day 1 of every cycle. The EORTC-QLQ-BR23 will be summarized at baseline and on Day 1 of every other cycle. Summary statistics for the change of each PRO measurement from baseline to the scheduled timepoint after baseline will be provided.

9.3.3.7. Pharmacokinetic Analyses

The drug concentration-time data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum) according to treatment.

Population PK assessment and exposure-response analyses will be conducted with pooled data from other studies, analyzed and reported separately. The analyses will be performed in accordance with regulatory guidance. The detailed procedures for the population PK, including model development and evaluation, will be described in a Pharmacometric Analysis Plan. The results of the analyses will be summarized in a Pharmacometric Analysis Report, separate from the clinical study report of this study.

9.3.5. Interim Analyses

Not applicable.

9.4. Sample Size Determination

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%.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines applicable to the countries where the study is conducted
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

The decision of whether a formal protocol amendment is needed to accommodate administrative changes (ie, those not affecting the participant benefit/risk ratio) will be made in accordance with current ICH GCP Guidelines and all other applicable guidelines in the countries where the study is conducted. Administrative changes may be conveyed to study Investigators and sites via a protocol clarification letter compliant with applicable guidelines in the countries where the study is conducted. Protocols and any substantial amendments to the protocol will require approval from the Health Authority(ies), the IRB/IEC (for site initiation/implementation), and/or such other entity as required prior to initiation of the protocol or overall implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for overall conduct of the study at the site and adherence to requirements of 21 CFR (US), ICH GCP Guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and any subsequent amendments thereof, and all other applicable local regulations.

The Investigator or designee will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC, annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by the procedures of the IRB/IEC in accordance with the study safety reporting rules (refer to Section [10.3](#))

10.1.2. Financial Disclosure

Investigators and Subinvestigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The Investigator or their representative will explain the nature of the study, including the risks and benefits, to the participant in simple layperson's terms and will answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH Guidelines, privacy and data protection requirements, where applicable, the requirements of the study center, and the IRB/IEC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF if the rescreening occurs more than 28 days after the initial Screening.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB/IEC.

Original signed ICFs will be maintained at the site and be made available for inspection, as appropriate.

10.1.4. Data Protection

Participants will be assigned a unique pseudonymized participant number by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the pseudonymized identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used and disclosed by the Sponsor in accordance with local data protection law, the ICF, and any additional consents obtained from the participant.

The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The ICF must notify the participant that his/her/their medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate members of the IRB/IEC, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Data Safety Monitoring Board

The DSMB will be composed of independent expert(s) in the clinical aspects of the disease/patient population being studied, one or more biostatisticians, and one or more Investigators with expertise in current clinical study conduct.

A separate DSMB Charter document will outline the schedule of data review and define the deliberative process, any events that would trigger unscheduled reviews, stopping procedures that are consistent with the protocol, reporting and voting procedures, and the contents of reports at the conclusion of each meeting, and how the DSMB will vote as to whether the study should continue without change, be modified or be terminated.

Note: That while the DSMB may vote on recommendations, the study Sponsor maintains the final say on actions related to DSMB findings.

10.1.6. Dissemination of Clinical Study Data

A summary of the results of the clinical study together with a summary that is understandable to a layperson will be provided after the global end (or early termination) of the study in all countries concerned to ensure full availability of all clinical data under this protocol, within 12 months.

10.1.7. Data Quality Assurance

Quality tolerance limits for this study will be predefined and filed in the eTMF to identify systematic issues that can impact participant safety and/or reliability of study results.

These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

10.1.7.1. Study Monitoring

Qualified representatives of the Sponsor or Sponsor designees (study monitors) will monitor the study according to a predetermined monitoring plan. The Investigator agrees to give study monitors direct access to all relevant study materials and permit their periodic review of all eCRFs and source documents supporting the participation of each participant in the study.

The eCRFs and other documentation supporting the study must be kept up to date by the Investigator and the staff at the study site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the Sponsor, at each monitoring visit (onsite or remote) and must be provided in a way such that the participant's confidentiality is maintained in accordance with local institution, state, country, and federal requirements.

10.1.7.2. Audits and Inspections

At some point during or after the study, an audit may be performed by appropriately qualified personnel from the Sponsor's Quality Assurance group, or their authorized representative. During any such audit, the Investigator agrees to give the auditor direct access to all relevant documents supporting the eCRFs and other study-related documents and to discuss any findings with the auditor.

Additionally, a representative from a regulatory agency may visit the Investigator at any point during or after the study to conduct an inspection of the study and the site. In the event of any such inspection, the Investigator agrees that the Sponsor would be notified and agrees to give the inspector direct access to all relevant documents and to discuss any findings with the inspector.

10.1.7.3. Quality Control and Quality Assurance

Applicable eCRF pages must be completed for each participant enrolled. Each completed eCRF, as well as records for those participants who discontinue the study, will require a signature by the principal Investigator at the study site. If a participant withdraws from the study, the reason must be noted on the eCRF (eg, if a participant is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome). The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

Accurate and reliable data collection will be assured by verification and cross-check activities (eg, the study monitor checking representative eCRFs against the Investigator's records [source document verification]), and maintenance of a drug-dispensing log by the Investigator.

Review of eCRFs, and validation/edit checks to identify and resolve discrepancies, will be performed throughout the study.

Investigator signatures will be collected upon completion of eCRF review. Electronic case report forms are not considered a study data source, but are used to record participant data relating to the study.

The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF. Guidance on completion of eCRFs will be provided in a separate technical document.

The Investigator must permit study audits and inspections according to Sponsor, IRB/IEC, and regulatory requirements and must provide direct access to source data documents.

Monitoring details describing strategies, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

All study data in this clinical study will be captured and stored in a 21 CFR Part 11-compliant system.

All relevant data generated by the participants in the study will be captured via an electronic PRO (ePRO) device that is 21 CFR Part 11-compliant. This device will be considered a study data source.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8.1. Records Retention

After closure of the study, the Investigator will maintain copies of all study records (ie, Investigator files and participant files) in a secure location.

The Investigator's study file will contain the protocol, protocol amendments, eCRF and query forms, IRB/IEC approval with correspondence, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Participant clinical source documents may include (but are not limited to) participant hospital records, physician's and nurse's notes, original laboratory reports, ECGs, electroencephalograms, X-rays, signed ICFs, consultant letters, and participant Screening and enrollment logs.

These documents must be kept on file by the Investigator for a period of 2 years following the date the marketing application is approved for the drug indication for which it is being investigated, or as otherwise specified by local regulations.

If no application is to be filed or if the application is not approved for such indication, all records pertaining to the conduct of the clinical study must be adequately maintained until 2 years after the investigation is discontinued and the regulatory authorities are notified, or as otherwise specified by local regulations. After the required period of time, the documents may be destroyed, subject to local regulations upon approval of the Sponsor.

The Investigator must not destroy any records associated with the study without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records and should notify the Sponsor of any reassignment of study records to another party or move to another location.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

10.1.9.2. Study Termination

The entire study may be terminated in the event of any of the following:

- Occurrence of AEs unknown to date with respect to their nature, severity, and duration, or the unexpected incidence of known AEs
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of participants
- Cancellation of the drug development program
- Sponsor decision for any other reason, as defined in Section 4.4

The Sponsor reserves the right to terminate the study at any time. If the study is terminated by the Sponsor, participants will not be provided further study intervention or study-supplied concomitant medication.

10.1.9.3. Site Termination

The Sponsor or designee reserves the right to close study sites or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Principal Investigator may initiate study-site closure at any time and shall notify the Sponsor in advance of the intended termination.

Reasons for the early closure of a study site may include, but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC, local Health Authorities, the Sponsor's procedures, or GCP Guidelines
- Inadequate or no recruitment of participants by the Investigator
- Total number of participants included earlier than expected

In the event of premature termination or suspension, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform each participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/IEC/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive approval from the IRB/IEC/Competent Authorities prior to implementation (if appropriate). In the US: Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

The decision of whether a formal protocol amendment is needed to accommodate administrative changes (ie, those not affecting the participant benefit/risk ratio) will be made in accordance with all applicable guidelines in the countries where the study is conducted.

Administrative changes may be conveyed to study Investigators and sites via a protocol clarification letter compliant with all applicable guidelines.

All protocol amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.12. Liability and Insurance

The Sponsor will take out third-party liability insurance coverage in accordance with all legal requirements.

The civil liability of the Investigator, the persons instructed by the Investigator and the hospital, practice, or institute in which they are employed, and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for participants taking part in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.13. Access to Source Data

As noted in Section [10.1.7.1](#), a monitor will perform remote or onsite visits during the study to review protocol compliance, compare eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. Electronic case report form entries will be verified with source documentation. The Investigator must provide direct access to all relevant study materials and permit their review by the study monitor and/or other qualified representatives of the Sponsor at each monitoring visit (onsite or remote). The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study.

As noted in Section [10.1.7.2](#), direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

The Investigator assures the Sponsor — and any CRO or other individual or entity working on the Sponsor's behalf, if involved in monitoring/data management — of the necessary support at all times.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in [Table 9](#) will be performed by the local laboratory.

Study-specific requirements for inclusion or exclusion of participants are detailed in [Section 5.1](#) and [Section 5.2](#), respectively, of this protocol.

Additional tests may be performed at any time during the study as determined necessary by Investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 9: Protocol-required Safety Laboratory Tests

| Laboratory Tests (as detailed in the SoA [Table 1]) | Parameters | |
|---|---|--|
| Hematology | Platelet count RBC count Hemoglobin Hematocrit RBC indices: <i>Mean corpuscular volume</i> <i>Mean corpuscular hemoglobin</i> <i>% Reticulocytes</i> | WBC count with differential: <i>Neutrophils</i> <i>Lymphocytes</i> <i>Monocytes</i> <i>Eosinophils</i> <i>Basophils</i> |
| Clinical Chemistry^a | BUN Potassium Creatinine Sodium Glucose (fasting) Calcium Chloride Inorganic phosphorous | AST/SGOT Total bilirubin, direct and indirect bilirubin ALT/SGPT Total protein Alkaline phosphatase ^b Lactate dehydrogenase Albumin |
| Routine Urinalysis | Specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes, hemoglobin by semiquantitative dipstick If urine result is abnormal (defined as blood > 0 or protein ≥ +1), microscopic sediment examination will be performed. Note: For all urine microscopy, sites are to collect the following information at minimum: hyaline casts, granular casts, epithelial cells, bacteria, WBCs, and RBCs, as applicable. | |
| Pregnancy Testing | Highly sensitive serum or urine β-hCG pregnancy test (for female participants of childbearing potential only; refer to Appendix 4) at timepoints detailed in the SoA (Table 1). | |
| Other Tests (refer to the SoA [Table 1]) | Follicle-stimulating hormone and estradiol (as needed in female participants of nonchildbearing potential only) Fasting lipid panel (total cholesterol, low-density lipoprotein, triglycerides, high-density lipoprotein) | |

| Laboratory Tests (as detailed in the SoA [Table 1]) | Parameters |
|---|--|
| | Coagulation (prothrombin time/INR, partial thromboplastin time, D-dimer, fibrinogen) |

^a. All events of ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN ($> 35\%$ direct bilirubin) or ALT or AST $\geq 3 \times$ ULN and INR > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's Law), must be reported to EQRx International, Inc. in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

^b. If alkaline phosphatase is elevated, consider fractionating.

β -hCG = human beta chorionic gonadotropin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; SoA = schedule of activities; ULN = upper limit of normal; WBC = white blood cell.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

| AE Definition |
|--|
| <ul style="list-style-type: none"> • An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. |
| Events <u>Meeting</u> the AE Definition |
| <ul style="list-style-type: none"> • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, per se, will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. |
| Events <u>NOT Meeting</u> the AE Definition |
| <ul style="list-style-type: none"> • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen |

10.3.2. Definition of SAE

| |
|---|
| An SAE is an AE that: |
| 1. Results in death |
| 2. Is life-threatening <ul style="list-style-type: none">• The term <i>life-threatening</i> in the definition of <i>serious</i> refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| 3. Requires inpatient hospitalization or prolongation of existing hospitalization <ul style="list-style-type: none">• In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.• Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| 4. Results in persistent or significant disability/incapacity <ul style="list-style-type: none">• The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.• This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| 5. Is a congenital anomaly/birth defect |
| 6. Other situations <ul style="list-style-type: none">• Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.• Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of drug dependency or drug abuse. |

10.3.3. Recording and Follow-up of AE or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information using the AE/SAE Form and the AE section of the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to EQRx International, Inc. and Parexel Pharmacovigilance Group in lieu of completion of the SAE Form.
- There may be instances when copies of medical records for certain cases are requested by both EQRx International, Inc. and Parexel Pharmacovigilance Group. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to EQRx International, Inc. and Parexel Pharmacovigilance Group.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The intensity of AEs should be documented using NCI CTCAE version 5.0.
- For events **not listed** in the NCI CTCAE version 5.0, the intensity of AEs should be classified according to the following categories:
 - **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
 - **Grade 2:** Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
 - **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden)
 - **Grade 4:** Life-threatening consequences; urgent intervention indicated
 - **Grade 5:** Death related to AE
- An event is defined as “serious” when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

| Assessment of Causality |
|--|
| <ul style="list-style-type: none">• The Investigator will assess the relationship between study intervention and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study intervention will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to study intervention, should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution: |
| <ul style="list-style-type: none">– Not related: The event is clearly related to other factors, such as the participant's environment or clinical state, therapeutic interventions, or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the study intervention.– Unlikely related: The temporal association, participant history, and/or circumstances are such that study intervention is not likely to have had an association with the observed event. Other conditions, including concurrent illness, progression, or expression of the disease state, or reaction to a concomitant drug administered appear to explain the event.– Possibly related: The event follows a reasonable temporal sequence from the time of study intervention administration or follows a known response to the study intervention but could have been produced by other factors, such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.– Probably related: The event follows a reasonable temporal sequence from the time of study intervention administration and follows a known response to the study intervention and cannot be reasonably explained by other factors, such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.– Definitely related: The event follows a reasonable temporal sequence from the time of study intervention administration or control abates upon discontinuation or cannot be explained by known characteristics of the participant's clinical state. |

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide BOTH EQRx International, Inc. and Parexel Pharmacovigilance Group with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The Investigator will submit any updated SAE data via email to BOTH drugsafety@eqrx.com and EQRxSafety@parexel.com within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

Definition of a Serious Adverse Event

- An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up) and at any dose of study intervention (active or placebo) that fulfills one or more of the following:
 - It results in death.
 - It is immediately life-threatening.
 - It requires formal inpatient hospitalization or prolongation of existing hospitalization.
 - It results in persistent or significant disability or incapacity.
 - It results in a congenital abnormality or birth defect.
 - It is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.
 - Important medical events that may not be one of the above may be considered an SAE by the Investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the participant, or may require medical or surgical intervention to prevent one of the outcomes listed above.
 - An AE is considered “life-threatening” if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

SAE Reporting via Email

- The Investigator must report any SAEs via email to BOTH drugsafety@eqrx.com and EQRxSafety@parexel.com within 24 hours of becoming aware of the event.
- The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report, and the Sponsor/Sponsor's designated agent will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (Investigator's Brochure or Summary of Product Characteristics). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.
- After the study is completed at a given site, the electronic data collection tool will be deactivated to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data capture system has been deactivated, then the site can report this information on a paper SAE Form or by telephone.
- Contacts for SAE reporting (as detailed in Section 10.3.4.1) can also be found in the Investigator site file.

SAE Reporting via SAE Form

- Email transmission of the SAE Form is the preferred method to transmit this information.
- In rare circumstances and in the absence of email equipment, notification by telephone is acceptable.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE Form within the designated reporting timeframes.
- Contacts for SAE reporting (as detailed in Section 10.3.4.1) can also be found in the Investigator site file.

Serious Unexpected Serious Adverse Reactions

Any AE that is serious, associated with the use of the study intervention, unexpected, and which has a reasonable suspected causal relationship to the study intervention is considered a SUSAR and has additional reporting requirements, as described below.

- An unexpected AE is an event or reaction that is not listed in the IB or not listed at the specificity or severity that has been observed, or the nature and severity of which is not consistent with the information about the medicinal product in question as set out in the reference safety information; or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the relevant current Investigational New Drug Application.
- A reasonable suspected causal relationship means that there is a reasonable possibility that the study intervention caused the AE, ie, evidence to suggest a causal relationship.
- If the SUSAR is fatal or life-threatening, associated with study intervention, and unexpected, regulatory authorities and IRBs/IECs will be notified as soon as possible and in any event within 7 calendar days after the Sponsor first learns of the event or such earlier time period as required under national law.
- Additional follow-up information for fatal or life-threatening SUSARs (eg, cause of death, autopsy report, hospital report) information should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with study intervention, and unexpected, regulatory authorities and IRBs/IECs will be notified as soon as possible and in any event within 15 calendar days after the Sponsor first learns of the event or such earlier time period as required under national law.
 - Additional follow-up information for non-fatal/life-threatening SUSARs (eg, hospital report) should be reported within 15 days total.
- The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of study participants. Follow-up information may be submitted if necessary.
- The Sponsor will also provide annual safety updates to the regulatory authorities and IRBs/IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

10.3.4.1. SAE Contact Details

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

Parexel International Corporation

Parexel Safety Services

Telephone Number: +1-781-434-5010

Parexel International Email: EQRxSafety@parexel.com

EQRx Safety Email: drugsafety@eqrx.com

Email the SAE form and any supporting documentation to BOTH EQRxSafety@parexel.com AND drugsafety@eqrx.com within 24 hours of becoming aware of the event.

Following receipt of the SAE Form, Parexel will provide a confirmation of receipt, which should be filed with the safety report. If you do not receive a confirmation of receipt within 3 working days, please re-submit the SAE report.

If email is down, a Parexel Safety Contact may be reached through Parexel's 24-hour voicemail box at +1-781-434-5010. Please leave the following information in your voicemail message:

- *Your name*
- *The telephone number where you can be reached*
- *The study protocol number and title*
- *The study intervention name*
- *The Principal Investigator's name*
- *The name of the Sponsor's pharmaceutical company*

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Study participants in the following categories are considered **female participants of childbearing potential (fertile/of reproductive potential)**:

1. Following menarche.
2. From the time of menarche until becoming **postmenopausal**, unless **permanently sterile** (see below).
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
 - Female participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
 - **Permanent sterilization** methods (for the purposes of this study) are defined as the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Notes:

- Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

10.4.2. Contraception Guidance

Note: The study exclusion criteria (Section 5.2) prohibit use of systemic estrogen, including hormonal contraception containing estrogen, in this study. Nonestrogen hormonal contraception, including progestogen-containing contraception, is permitted at Investigator discretion.

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| CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE: |
| Highly Effective Methods^b that Have Low User Dependency <i>Failure rate of < 1% per year when used consistently and correctly.</i> |
| <p>For female study participants of childbearing potential and male study participants' female partners who are of childbearing potential (as applicable):</p> <ul style="list-style-type: none"> • Implantable progestogen-only hormone contraception associated with inhibition of ovulation^c <ul style="list-style-type: none"> – Intrauterine device – intrauterine hormone-releasing system^c – Bilateral tubal occlusion |
| Highly Effective Methods^b that are User-Dependent <i>Failure rate of < 1% per year when used consistently and correctly.</i> |
| <p>For female study participants of childbearing potential and male study participants' female partners who are of childbearing potential (as applicable):</p> <ul style="list-style-type: none"> • Non-estrogen hormonal contraception (progestogen-containing contraception is permitted at Investigator discretion) associated with inhibition of ovulation^c <ul style="list-style-type: none"> – oral – intravaginal – transdermal – injectable |
| <ul style="list-style-type: none"> • Progestogen-only hormone contraception associated with inhibition of ovulation^c <ul style="list-style-type: none"> – oral – injectable |
| <p>For female study participants of childbearing potential:</p> <ul style="list-style-type: none"> • Sexual abstinence <p><i>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention.</i></p> <p><i>The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</i></p> |

| |
|---|
| <p>Effective Methods^d that are Not Considered Highly Effective <i>Failure rate of $\geq 1\%$ per year when used consistently and correctly.</i></p> <p>For female study participants of childbearing potential and male study participants' female partners who are of childbearing potential (as applicable):</p> <ul style="list-style-type: none"> • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)^c <ul style="list-style-type: none"> – Note: Male participants with female partners who are of childbearing potential are to use a male condom throughout their study treatment and for at least 365 days (1 year) after the last dose of any study intervention, even if azoospermic (whether vasectomized or due to a medical cause). • Cervical cap, diaphragm, or sponge with spermicide |
| <p>Additional Contraception Guidance During and for at Least 1 Year after Treatment with Fulvestrant</p> <p>For male study participants:</p> <ul style="list-style-type: none"> • Highly effective contraception is to be used during treatment with fulvestrant and for at least 365 days (1 year) after the last dose of fulvestrant, as recommended in the FDA-approved prescribing information (FASLODEX[®] (fulvestrant), rev. 05/2019). <p>For female study participants of childbearing potential:</p> <ul style="list-style-type: none"> • Highly effective contraception is to be used during treatment with fulvestrant and for at least 365 days (1 year) after the last dose of fulvestrant, as recommended in the FDA-approved prescribing information (FASLODEX[®] (fulvestrant), rev. 05/2019). |
| <p>Additional Contraception Guidance During and for 12 Weeks after Treatment with Goserelin</p> <p>For female study participants of childbearing potential:</p> <ul style="list-style-type: none"> • Highly effective nonhormonal contraception is to be used during treatment with goserelin and for 12 weeks after the last dose of goserelin, as recommended in the FDA-approved prescribing information (ZOLADEX[®] [goserelin], rev. 02/2015). |

^a. Contraceptive use by female and male study participants should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

^b. Failure rate of $< 1\%$ per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

^c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG Guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

^d. Considered effective, but not highly effective – failure rate of $\geq 1\%$ per year.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

CTFG = Clinical Trial Facilitation Group; FDA = Food and Drug Administration; LAM = lactational amenorrhea method.

10.5.1. EORTC-QLQ-C30

19011581



31

Please go on to the next page

During the past week:

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

1 2 3 4 5 6 7

Excellent

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|

Excellent

10.5.2. EORTC-QLQ-BR23

ENGLISH



EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|------------|----------|-------------|-----------|
| 31. Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 32. Did food and drink taste different than usual? | 1 | 2 | 3 | 4 |
| 33. Were your eyes painful, irritated or watery? | 1 | 2 | 3 | 4 |
| 34. Have you lost any hair? | 1 | 2 | 3 | 4 |
| 35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair? | 1 | 2 | 3 | 4 |
| 36. Did you feel ill or unwell? | 1 | 2 | 3 | 4 |
| 37. Did you have hot flushes? | 1 | 2 | 3 | 4 |
| 38. Did you have headaches? | 1 | 2 | 3 | 4 |
| 39. Have you felt physically less attractive as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 40. Have you been feeling less feminine as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 41. Did you find it difficult to look at yourself naked? | 1 | 2 | 3 | 4 |
| 42. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 43. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |
| During the past <u>four</u> weeks: | Not at All | A Little | Quite a Bit | Very Much |
| 44. To what extent were you interested in sex? | 1 | 2 | 3 | 4 |
| 45. To what extent were you sexually active? (with or without intercourse) | 1 | 2 | 3 | 4 |
| 46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you? | 1 | 2 | 3 | 4 |

Please go on to the next page.

ENGLISH

| During the past week: | | Not at All | A Little | Quite a Bit | Very Much |
|-----------------------|---|---------------|-------------|----------------|--------------|
| 47. | Did you have any pain in your arm or shoulder? | 1 | 2 | 3 | 4 |
| 48. | Did you have a swollen arm or hand? | 1 | 2 | 3 | 4 |
| 49. | Was it difficult to raise your arm or to move it sideways? | 1 | 2 | 3 | 4 |
| 50. | Have you had any pain in the area of your affected breast? | 1 | 2 | 3 | 4 |
| 51. | Was the area of your affected breast swollen? | 1 | 2 | 3 | 4 |
| 52. | Was the area of your affected breast oversensitive? | 1 | 2 | 3 | 4 |
| 53. | Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)? | 1 | 2 | 3 | 4 |

10.5.3. EQ-5D-5L



Health Questionnaire

English version for the UK

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

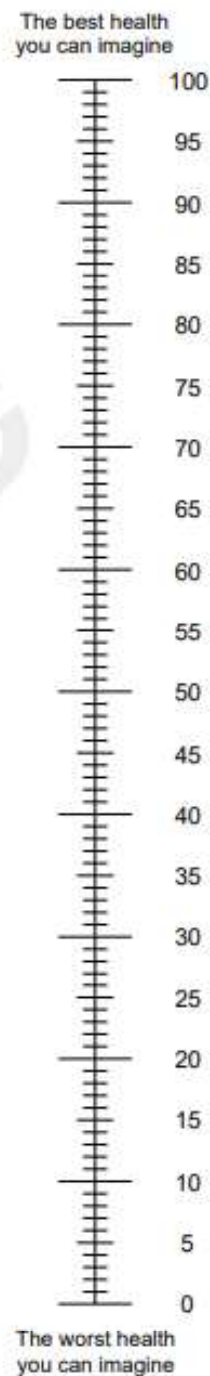
- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

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

YOUR HEALTH TODAY =



10.5.4. FACIT Item GP5

GP5 (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

| | Not at all | A little bit | Some- what | Quite a bit | Very much |
|--|---------------|-----------------|---------------|----------------|--------------|
| <div><div>GP5</div></div> I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |

10.6. Appendix 6: Abbreviations

| Abbreviation | Description |
|----------------------|---|
| β-hCG | Human beta chorionic gonadotrophin |
| 1L | First-line |
| 2L | Second-line |
| ADL | Activities of daily living |
| AE | Adverse event |
| AI | Aromatase inhibitor |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| AUC _{0-inf} | Area under the concentration-time curve extrapolated to infinity |
| AUC _{0-t} | Area under the concentration-time curve from time zero to the last observable concentration |
| BCRP | Breast cancer resistance protein |
| BID | Twice daily |
| C1D1 | Cycle 1 Day 1 |
| CBR | Clinical benefit rate |
| CDK | Cyclin-dependent kinase |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| C _{max} | Maximum plasma concentration |
| CNS | Central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| CR | Complete response |
| CRO | Clinical research organization |
| CT | Computed tomography |
| CTFG | Clinical Trial Facilitation Group |
| CYP | Cytochrome P450 |
| DDI | Drug-drug interaction |
| DLCO | Diffusing capacity of the lung for carbon monoxide |
| DOR | Duration of response |
| DSMB | Data Safety Monitoring Board |

| Abbreviation | Description |
|---------------------|---|
| DSUR | Development safety update report |
| ECG | Electrocardiogram |
| ECOG PS | Eastern Cooperative Oncology Group performance status |
| eCRF | Electronic case report form |
| ED | Early Discontinuation |
| EDC | Electronic data capture |
| EGFR | Epidermal growth factor receptor |
| EORTC-QLQ-C30 | European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core |
| EORTC-QLQ-BR23 | European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Breast |
| EOT | End of treatment |
| EQ-5D-5L | EuroQoL 5-dimension 5-level questionnaire |
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials Database |
| ER | Estrogen receptor |
| FACIT | Functional Assessment of Chronic Illness Therapy |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FDG-PET | Negative positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte colony-stimulating factor |
| HER2- | Human epidermal growth factor 2-negative |
| HIV | Human immunodeficiency virus |
| HMA | Heads of Medicines Agencies |
| HR+ | Hormone receptor-positive |
| HRT | Hormone replacement therapy |
| IB | Investigator's Brochure |
| IC ₅₀ | Half maximal inhibitory concentration |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |

| Abbreviation | Description |
|---------------------|--|
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IND | Investigational new drug |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IRT | Interactive response technology |
| IV | Intravenous |
| K_i | Inhibitory constant |
| K_{inact} | Inactivation rate constant |
| LD | Longest diameter |
| MATE1 | Multidrug and toxin extrusion 1 |
| MATE2-K | Multidrug and toxin extrusion 2-K |
| mBC | Metastatic breast cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| mRNA | Messenger ribonucleic acid |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NIMP | Non-investigational medicinal product |
| OCT1 | Organic cation transporter 1 |
| OCT2 | Organic cation transporter 2 |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progression of disease |
| PET | Positron emission tomography |
| PFS | Progression-free survival |
| P-gp | P-glycoprotein |
| PK | Pharmacokinetic(s) |
| PR | Partial response |
| PRO | Patient-reported outcome |
| PT | Preferred term |
| QD | Once daily |
| QoL | Quality of life |

| Abbreviation | Description |
|---------------------|---|
| QTL | Quality tolerance limit |
| Rb | Retinoblastoma protein |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAR | Serious adverse reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SD | Stable disease |
| SoA | Schedule of activities |
| SOC | System organ class |
| SOP | Standard operating procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{1/2}$ | Terminal phase elimination half-life |
| TEAE | Treatment-emergent adverse event |
| t_{max} | Time to maximum concentration |
| TTR | Time to response |
| ULN | Upper limit of normal |
| US | United States |
| WHO | World Health Organization |

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