Protocol: EQ132-201

A PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LEROCICLIB IN PARTICIPANTS WITH ADVANCED BREAST CANCER

Lerociclib (also known as EQ132, G1T38, and GB491)

Indication studied:	*First-line and second-line hormone receptor-positive/human epidermal growth factor 2-negative metastatic breast cancer*
Developmental phase of study:	*Phase 2*
First participant enrolled:	*22 December 2021*
Last participant completed:	*30 November 2023*
Rationale for the abbreviated clinical study report:	*Study EQ132-201 was terminated early by the Sponsor due to corporate changes at EQRx . The study was not stopped early for safety reasons or futility and it is not intended to contribute to the evaluation of product effectiveness or provide definitive information on clinical pharmacology.*
Release date of report:	*28 February 2024*
Company/Sponsor signatory:	*EQRx International, Inc.* *50 Hampshire Street* *Cambridge, MA 02139 USA*

This study was conducted in accordance with the ethical principles of GCP according to the ICH Harmonized Tripartite Guideline.

2. SYNOPSIS

Name of Sponsor/Company: EQRx International, Inc.	*(For National Authority Use Only)*
Name of Finished Product: Lerociclib	
Name of Active Ingredient: Lerociclib	
Title of Study: A Phase 2 Study to Evaluate the Safety and Efficacy of Lerociclib in Participants with Advanced Breast Cancer	
Principal Investigator: **Name:** Dr. Sibel Blau **Address:** Northwest Medical Specialties PLLC, 2940 S. Meridian, Puyallup, WA 98373 USA.	
Study centers: 21 centers in the following countries: Belgium, Georgia, Italy, Mexico, Moldova (Republic of), and the USA	
Publications (reference): Not applicable	

Name of Sponsor/Company: EQRx International, Inc.	*(For National Authority Use Only)*
Name of Finished Product: Lerociclib	
Name of Active Ingredient: Lerociclib	
Studied period (years): Study initiation date: 22 December 2021 Date last participant completed: 30 November 2023	**Phase of development:** Phase 2

Objectives:

Primary:

- To characterize the safety and tolerability of lerociclib in combination with endocrine therapy in participants with first-line (1L) and second-line (2L) hormone receptor positive (HR+)/human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (mBC).

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

Methodology:

Study EQ132-201 was a multicenter, single-arm, open-label clinical study intended to evaluate the safety and efficacy of lerociclib administered in combination with endocrine therapy (letrozole, fulvestrant, and/or goserelin) in female and male participants with HR+/HER2- mBC.

As presented in this abbreviated clinical study report, which uses a data cutoff date of 08 January 2024, the study population consisted of both metastatic newly diagnosed, treatment-naive participants with HR+/HER2- mBC (the 1L population) and participants with HR+/HER2- mBC who had 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 were required to have been on goserelin for at least 28 days prior to entering the study, and to remain on goserelin throughout their time on study in accordance with the prescribing information and according to the study site's standard practice.

The study was designed with 3 phases: a screening phase of up to 42 days in duration; a treatment phase (including a safety follow-up visit occurring 30 days after the last dose of lerociclib); and a post-treatment follow-up phase (including a survival follow-up phase) that was to continue until

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participant death, loss of follow-up, withdrawal of consent, or the end of the overall study (whichever occurred first).

Number of participants (planned and analyzed):

Approximately 100 study participants (~ 50 each in the 1L and 2L treatment arms) were planned for enrollment and dosing. A total of 100 participants (n = 54 in the 1L arm and n = 46 in the 2L arm) were actually enrolled and dosed (with non-investigational medicinal product [NIMP] or investigational medicinal product [IMP]) before the study was terminated by the Sponsor. These 100 participants comprised the Safety Analysis Set used for the safety analyses presented in this report.

Diagnosis and main criteria for inclusion:

Main inclusion criteria:

- Female or male participant, at least 18 years of age (or the legal age of consent in the applicable jurisdiction) at the time of giving signed informed consent, with histologically and/or cytologically confirmed diagnosis of estrogen receptor-positive and/or progesterone receptors-positive breast cancer by local laboratory.
- Breast cancer is HER2- and advanced (locoregionally recurrent; not amenable to curative therapy, e.g., surgery and/or radiotherapy; or metastatic) and meets one of the following additional criteria:
    - Newly diagnosed advanced/metastatic disease (treatment-naive).
    - Documented evidence of relapse following neoadjuvant (adjuvant) endocrine therapy, with no treatment received for advanced/metastatic disease.
    - Documented evidence of relapse following completion of adjuvant endocrine therapy, followed by subsequent documented progression after 1 line of endocrine therapy (with either tamoxifen or an aromatase inhibitor [AI]) for advanced/metastatic disease.
    - Newly diagnosed advanced/metastatic disease at diagnosis, with documented evidence of progression after 1 line of endocrine therapy (with tamoxifen, exemestane, or an AI).
- Eastern Cooperative Oncology Group performance status of 0 or 1.

Main exclusion criteria:

- Symptomatic visceral disease or any disease burden rendering the participant ineligible for endocrine therapy per the Investigator's best judgment.
- Peritoneal carcinomatosis.
- Inflammatory breast cancer at the time of Screening.

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- Cancer had central nervous system (CNS) involvement, unless participant is at least 4 weeks from prior therapy completion to starting study intervention; has stable CNS tumor at the time of Screening; and is not receiving steroids and/or enzyme-inducing anti-epileptic medications for brain metastases.
- History of prior treatment with chemotherapy (except neoadjuvant/adjuvant chemotherapy), any Cyclin-dependent kinase 4/6 inhibitor, or fulvestrant.
- Use of systemic estrogens (e.g., hormonal contraception, hormone replacement therapy).

Test product, dose and mode of administration, batch numbers:

- Lerociclib (IMP), administered orally twice daily in tablet form at 50 mg or 150 mg (or as otherwise directed per the dose modification section [Section 6.5] of the protocol [provided in Appendix 11.1.1], as applicable).

Test product batch numbers are available upon request.

Reference therapies (NIMP), doses and modes of administration, batch numbers:

- Letrozole, administered orally once daily in tablet form at 2.5 mg.
- Fulvestrant, administered as an intramuscular injection, once every 2 weeks for the initial 3 doses and then once every 4 weeks (Q4W) thereafter, at 500 mg.
- ZOLADEX, a goserelin acetate implant (for pre- or perimenopausal female participants and male participants only) administered subcutaneously Q4W at 3.6 mg.

Reference therapy batch numbers are available upon request.

Duration of treatment:

Until disease progression as determined by the Investigator per Response Evaluation Criteria in Solid Tumors (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 occurred first.

Criteria for evaluation:

Safety:

Primary endpoint:

- Incidence of adverse events (AEs) and serious adverse events (SAEs).

Secondary endpoints:

- Change from baseline in clinical laboratory parameters (hematology, clinical chemistry, coagulation, fasting lipid panel, and urinalysis).
- Change from baseline in vital signs and 12-lead electrocardiogram (ECG) parameters.

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Efficacy:

Secondary endpoints:

- Objective response rate, defined as the proportion of participants with a best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by the Investigator.
- Clinical benefit rate, defined as the proportion of participants with a best overall response of CR, PR, or Stable disease (SD) (for at least 8 weeks) according to RECIST v1.1 as assessed by the Investigator.
- Progression-free survival (PFS), defined as the time from first dose of lerociclib until the date of documented progressive disease (PD) or death, according to RECIST v1.1 as assessed by the Investigator.
- Overall survival (OS), defined as the time from the date of first dose of lerociclib to the date of death due to any cause.
- Duration of response, 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 the Investigator.
- Time to response, defined as the time from first dose of lerociclib until the first documented response (CR or PR).

As the Sponsor terminated the study early, limited data other than safety data were collected and neither QoL nor PK analyses were performed.

Statistical methods:

The following study populations were initially planned for analysis per the protocol and statistical analysis plan:

- Safety Analysis Set, defined as all enrolled participants who received at least 1 dose of study intervention (NIMP or IMP). This population was used for all safety analyses performed.
- Full Analysis Set, defined as all enrolled participants who were exposed to lerociclib during the study. This population was intended for analyses of PFS, OS, and QoL.
- Response Evaluable Analysis Set, defined as all enrolled participants who were exposed to lerociclib during the study and who had measurable disease at baseline. This population was intended for analyses of tumor response endpoints.

In consideration of the premature termination of this study by the Sponsor, collection of data other than safety data was limited. The resulting data are not intended to support effectiveness of the product.

SUMMARY – CONCLUSIONS

SAFETY RESULTS:

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- Overall, 100 participants (n = 54 in the 1L population and n = 46 in the 2L population) were exposed to study intervention.
- A total of 6 (6%) participants experienced 12 treatment-emergent SAEs and 2 (2%) participants had 2 SAEs prior to receiving study intervention. The proportion of participants with SAEs were similar in both study populations.
- A total of 41 participants—23 (42.6%) in the 1L arm and 18 (39.1%) in the 2L arm—experienced at least 1 TEAE of Grade 3 or higher severity. One participant in the 1L arm had an AE of Grade 5 severity.
- At a system organ class level, the most common treatment-emergent AEs (TEAEs) were 'Investigations' (53%), 'Gastrointestinal disorders' (52%), 'Blood and lymphatic system disorders' (37%), and 'General disorders and administration site conditions' and 'Infections and infestations' (both, 35%).
- Overall, the most common TEAEs were diarrhoea (35%), neutrophil count decreased (32%), nausea (29%), and anaemia, fatigue, and white blood cell count decreased (all, 25%). The proportion of participants reporting TEAEs were comparable between the two study populations.
- Overall, 8 (8%) participants died during the study. One (1%) participant in the 1L arm experienced a fatal SAE of pneumothorax, 5 participants (n= 3 in the 1L population and n = 2 in the 2L population) died due to progressive disease, and 1 participant in the 2L population died due to unknown cause. One (1.9%) participant in the 1L arm discontinued the study due to death. The site failed to complete the death form for the participant. A Note to File is submitted for this participant.
- A total of 86 participants (86%) had TEAEs related to study intervention. The proportion of participants reporting related-TEAEs were comparable between the two study populations.
- No clinically relevant trends were observed for any of the clinical laboratory parameters, vital signs measurements, or ECG parameters. Some values were reported outside the normal ranges; however, these were deemed as not clinically significant by the Investigator.

EVALUABLE EFFICACY RESULTS:

The evaluable efficacy data collected prior to the early termination of the study by the Sponsor are summarized in Table S1 and Table S2. Key findings based on the available data include the following:

- The objective response rate and clinical benefit rate in the Response Evaluable Analysis Set was higher in 1L population when compared with 2L population.
- A best response of PR was observed in 23.1% participants in the 1L population and 11.4% participants in the 2L population and a best response of SD was observed in 56.4% participants in the 1L population and 57.1% participants in the 2L population.

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- The estimated PFS rate up to 6 months with 95% confidence interval was 0.82 (57.35, 93.37) in the 1L population and 0.70 (46.72, 84.08) in the 2L population. For 12 and 18 months, the estimated PFS rate in the 2L population was not estimable.

Table S1 Summary of Best Overall Response, Objective Response Rate, and Clinical Benefit Rate (Response Evaluable Analysis Set)

	1L (N=39)	2L (N=35)
Best Overall Response		
CR (confirmed)	0	0
PR (confirmed)	9 (23.1)	4 (11.4)
SD	22 (56.4)	20 (57.1)
PD	4 (10.3)	8 (22.9)
NE	0	0
Non-CR/Non-PD	0	0
NED	0	0
ORR [1]	9 (23.1%)	4 (11.4%)
95% CI	(11.13%, 39.33%)	(3.20%, 26.74%)
CBR [2]	31 (79.5%)	24 (68.6%)
95% CI	(63.54%, 90.70%)	(50.71%, 83.15%)

Abbreviations: 1L = First-line population of newly diagnosed, treatment-naive participants with HR+/HER2- mBC; 2L = Second-line population of participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole; CBR = Clinical Benefit Rate; CI = Confidence interval; CR = Complete Response; ORR = Objective Response Rate; PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; NE = Not Evaluable; NED = No evidence of disease.
[1] ORR is defined as the percentage of participants achieving a confirmed CR or confirmed PR based on RECIST, v1.1.
[2] CBR is defined as the percentage of participants having achieved a confirmed CR, confirmed PR, or SD. The 95% CIs are calculated using the Clopper-Pearson method.
Source: Table 14.2.1.1.

Table S2 Kaplan-Meier Estimates for Progression-free Survival (Full Analysis Set)

	1L (N=54)	2L (N=46)
Number of Participants [n (%)]		
Events [1]	4 (7.4)	8 (17.4)
Censored	50 (92.6)	38 (82.6)
Time to Event (days) [2]		
Q1 (95% CI)	NE (NE, NE)	64.00 (61.00, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	2, 560	2, 229
Probability of Progression-free Survival (95% CI) [3]		
Up to 6 Months	0.82 (57.35, 93.37)	0.70 (46.72, 84.08)
Up to 12 Months	0.82 (57.35, 93.37)	NE (NE, NE)
Up to 18 Months	0.82 (57.35, 93.37)	NE (NE, NE)
Up to 24 Months	NE (NE, NE)	NE (NE, NE)
Up to 30 Months	NE (NE, NE)	NE (NE, NE)
Up to 36 Months	NE (NE, NE)	NE (NE, NE)
Up to 42 Months	NE (NE, NE)	NE (NE, NE)

Abbreviations: 1L = First-line population of newly diagnosed, treatment-naive participants with HR+/HER2- mBC; 2L = Second-line population of participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole; CI = Confidence interval; NE = Not estimable; Q1 = First quartile; Q3 = Third quartile.
[1] An event is defined as progression of disease based on RECIST, v1.1 or death.
[2] Estimates are from a Kaplan-Meier analysis.
[3] The 95% CIs are calculated using the log-log transformation.
A month is defined as 28 days or 1 cycle.
Source: Table 14.2.2.1.1.

CONCLUSIONS:

Overall, 115 participants were screened to enroll 100 participants (n = 54 in the 1L arm and n = 46 in the 2L arm) in the study. All participants were discontinued from the study primarily due to study termination by Sponsor (83%). Overall, 96 participants experienced at least 1 TEAE during the study, the majority of the participants (55%) had AEs of Grade 1 or 2. Six participants experienced at least 1 treatment-emergent SAE, out of which one was fatal. Overall, 8 (8%) participants died during the study mainly due to progressive disease. Most of the participants (86%) experienced at least 1 TEAE related to study intervention, and the proportion of participants reporting related-TEAEs were comparable between the two study populations.

Date of the report: 28 February 2024

3. TABLE OF CONTENTS FOR THE ABBREVIATED CLINICAL STUDY REPORT

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialized terms are used in this study report.

Abbreviation	Definition
1L	First-line
2L	Second-line
AE	Adverse event
AI	Aromatase inhibitor
CBR	Clinical benefit rate
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
ECG	Electrocardiogram
EORTC-QLQ-BR	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Breast
FDA	Food and Drug Administration
HMA	Heads of Medicines Agencies
HRT	Hormone replacement therapy
HR+	hormone receptor-positive
HER2-	human epidermal growth factor 2-negative
IMP	Investigational medicinal product
mBC	metastatic breast cancer
MRI	Magnetic resonance imaging
NIMP	Non-investigational medicinal product
NE	Not evaluable
NED	No evidence of disease
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival

Abbreviation	Definition
PK	Pharmacokinetic(s)
PR	Partial response
Q1	First quartile
Q3	Third quartile
Q4W	Once every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
USA	United States of America

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan: Description

Study EQ132-201 was designed as a multicenter, single-arm, open-label clinical study. The study was intended to evaluate the safety and efficacy of lerociclib administered in combination with standard endocrine therapy in female and male participants with hormone receptor-positive (HR+)/human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (mBC).

The study population comprised both newly diagnosed, treatment-naive participants with HR+/HER2- mBC (collectively referred to as the first-line [1L] population) and participants with HR+/HER2- mBC who had already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole (collectively referred to as the second-line [2L] population).

Approximately 100 participants (~ 50 each in the 1L and 2L arms) were originally planned to be enrolled and dosed in the study. All premenopausal or perimenopausal female participants and all male participants were required to be receiving goserelin for at least 28 days prior to study entry and to 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 was decoupled from the rest of the study visit schedule and was instead determined by the date of the participant's most recent dose of goserelin at study entry (with "goserelin Cycle 1 Day 1" 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) were to receive the Investigator's choice of aromatase inhibitor (letrozole) or fulvestrant, plus lerociclib 150 mg twice daily. All participants were to be treated according to the best current practice guidelines and standard of care within each institution or country where the study was conducted.

The study consisted of 3 phases: a Screening Phase of up to 42 days in duration; a Treatment Phase (which included a Safety Follow-up Visit occurring 30 days after the last dose of lerociclib); and a Post-Treatment Follow-up Phase (which included a Survival Follow-up Phase).

While receiving lerociclib, participants were to 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, and every 12 weeks thereafter. All participants were also to undergo a bone scan at baseline and annually thereafter (or as per the Investigator's standard of care). If bone disease was identified, participants were to undergo whole-body bone scans every 8 weeks for the first 12 months and then every 12 weeks thereafter. Optional imaging modalities included 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 were to continue therapy until disease progression as determined by the Investigator per Response Evaluation Criteria in Solid Tumors (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 occurred first.

5.2. Changes in the Conduct of the Study or Planned Analyses

As previously noted, this study was terminated early by the Sponsor; therefore, limited data were available for the protocol- and statistical analysis plan-specified analyses. Full safety data are summarized in Section 7 and limited efficacy data are summarized in Section 8. No Quality-of-Life or Pharmacokinetic analyses were performed.

The key modifications made to the study protocol via the 5 total protocol amendments are summarized below in **Error! Reference source not found.**. The original protocol and all amendments, including the Summaries of Changes for the latter, are included in Appendix 11.1.1.

Table 1 Summary of Amendments to the Protocol

Protocol Version # (Amendment #), Date	Summary of Key Modifications Reflected in the Amendment
Version 3.0 (Amendment 3), 27 February 2023	• Global 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 CTFG.
Version 2.2 (Amendment 2.2 [Italy-specific]), 24 October 2022	• Italy-specific 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 CTFG.
Version 2.1 (Amendment 2.1 [Belgium-specific]), 25 April 2022	• Belgium-specific 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 CTFG.
Version 2.0 (Amendment 2), 10 November 2021	• Incorporation of broader language (i.e., "participants" instead of "women") where applicable throughout the protocol to allow the enrollment of male participants who meet relevant eligibility criteria. • New exclusion criterion for use of systemic estrogens (e.g., hormonal contraception, HRT). • New language advising the use of highly effective contraception during treatment with fulvestrant and for 1 year after the last dose, and the use of highly effective nonhormonal contraception during treatment with goserelin and for 12 weeks

Protocol Version # (Amendment #), Date	Summary of Key Modifications Reflected in the Amendment
	after the last dose, in female participants who are WOCBP, as recommended in the FDA-approved prescribing information for fulvestrant and goserelin. • New criteria (and corresponding protocol section) for potential stoppage/discontinuation of the overall study. • New 12-lead ECG collection timepoint at Day 1 of Cycle 3.
Version 1.1 (Amendment 1), 02 September 2021	• Replacement of the EORTC-QLQ-BR45 QoL instrument with the EORTC-QLQ-BR23 instrument for breast cancer patients, as translations of the latter are more widely available.

Abbreviations: ECG = Electrocardiogram; EORTC-QLQ-BR = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Breast; FDA = Food and drug administration; HMA CTFG = Heads of Medicine Agency-Clinical Trials Facilitation Group; HRT = Hormone replacement therapy; QoL = Quality-of-life; WOCBP = Women of childbearing potential.

6. STUDY PARTICIPANTS

6.1. Disposition of Participants

A summary of participants' disposition is summarized in Table 2. A total of 115 participants were screened for enrollment in this study. Of these, 14 (12.2%) were determined to be screen failures. One (0.9%) was excluded from the study for other reasons prior to the first treatment.

A total of 100 participants (n = 54 in the 1L arm and n = 46 in the 2L arm) were ultimately enrolled in the study to receive study intervention prior to its early termination by the Sponsor. None of the participants had completed the study as of the 08 January 2024, data cutoff date used for this abbreviated clinical study report. Of the 100 participants—54 (100%) participants in the 1L arm and 46 (100%) participants in the 2L arm who were discontinued from the study, 83 (83%) participants (43 [79.6%] in the 1L arm and 40 [87%] in the 2L arm) had done so due to study termination by the Sponsor.

Table 2 Participant Disposition - (All Participants Screened)

	1L n (%)	2L n (%)	Total n (%)
Screened	62	53	115
Excluded Prior to First Treatment	8 (12.9)	7 (13.2)	15 (13.0)
Screen Failure	7 (11.3)	7 (13.2)	14 (12.2)
Other	1 (1.6)	0	1 (0.9)
Treated [1]	54 (87.1)	46 (86.8)	100 (87.0)
Withdrew from Treatment	53 (85.5)	46 (86.8)	99 (86.1)
Protocol Violation	0	0	0
Adverse Event	6 (9.7)	0	6 (5.2)
Death	0	0	0
Withdrawal by Participant	1 (1.6)	1 (1.9)	2 (1.7)
Lost to Follow-Up	1 (1.6)	0	1 (0.9)
Non-Compliance with Study Drug	0	0	0
Physician's Decision	1 (1.6)	1 (1.9)	2 (1.7)
Radiologic Progressive Disease	10 (16.1)	16 (30.2)	26 (22.6)
Clinical Progression	1 (1.6)	1 (1.9)	2 (1.7)
Study Terminated by Sponsor	30 (48.4)	26 (49.1)	56 (48.7)
Other	3 (4.8)	1 (1.9)	4 (3.5)
Withdrew from Study	62 (100)	53 (100)	115 (100)
Protocol Violation	0	0	0
Adverse Event	1 (1.6)	0	1 (0.9)
Death	5 (8.1)	3 (5.7)	8 (7.0)
Withdrawal by Participant	2 (3.2)	0	2 (1.7)
Lost to Follow-Up	1 (1.6)	2 (3.8)	3 (2.6)
Non-Compliance with Study Drug	0	0	0
Physician's Decision	1 (1.6)	0	1 (0.9)
Radiologic Progressive Disease	0	0	0
Clinical Progression	0	1 (1.9)	1 (0.9)
Screen Failure	7 (11.3)	7 (13.2)	14 (12.2)
Study Terminated by Sponsor	43 (69.4)	40 (75.5)	83 (72.2)
Other	2 (3.2)	0	2 (1.7)

Abbreviations: 1L = First-line population of newly-diagnosed, treatment-naive participants with HR+/HER2- mBC; 2L = Second-line population of participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole.
[1] Participants who received at least one dose of study medication.
[2] Participants are only included once at the highest cycle completed.
Percentages are calculated based on the number of participants screened.
Source: Table 14.1.1.

7. SAFETY EVALUATION

7.1. Extent of Exposure

A total of 100 participants (n = 54 in the 1L population and n = 46 in the 2L population) comprised the Safety Analysis Set, meaning they were exposed to study intervention (non-investigational medicinal product or investigational medicinal product) prior to early termination of the study by the Sponsor. Participant exposure to study intervention is summarized in Table 3.

Table 3 Summary of Exposure (Safety Analysis Population)

	1L (N=54) n (%)	**2L (N=46) n (%)**	**Total (N=100) n (%)**
Time on Treatment (days)			
n	54	46	100
Mean (SD)	269.7 (141.70)	199.5 (111.89)	237.4 (132.95)
Median	297.0	195.5	231.5
Min, Max	24, 531	45, 448	24, 531
Total Dose (mg) Received			
n	54	46	100
Mean (SD)	77325.9 (40846.87)	59369.6 (33075.29)	69066.0 (38358.59)
Median	85050.0	58650.0	67650.0
Min, Max	4350, 159300	13500, 134400	4350, 159300
Average Dose per Day (mg)			
n	54	46	100
Mean (SD)	289.3 (39.29)	298.5 (8.15)	293.5 (29.63)
Median	300.0	300.0	300.0
Min, Max	150.00, 407.77	245.19, 300.00	150.00, 407.77
Relative Dose Intensity			
n	54	46	100
Mean (SD)	1.0 (0.12)	1.0 (0.03)	1.0 (0.09)
Median	1.0	1.0	1.0
Min, Max	0.50, 1.00	0.82, 1.00	0.50, 1.00
Subjects with Dose Interruptions	7 (13.0)	3 (6.5)	10 (10.0)
Subjects with Dose Reductions	6 (11.1)	1 (2.2)	7 (7.0)
Subjects with Reduction to 200 mg	6 (11.1)	1 (2.2)	7 (7.0)
Subjects with Reduction to 150 mg	1 (1.9)	0	1 (1.0)
Number of Dose Reductions	10	1	11
Number of Dose Reductions to 200 mg	6	1	7
Number of Dose Reductions to 150 mg	4	0	4
Number of Treatment Discontinuations	33 (61.1)	19 (41.3)	52 (52.0)

Abbreviations: 1L = First-line population of newly diagnosed, treatment-naive participants with HR+/HER2- mBC; 2L = Second-line population of participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole; Min = Minimum; Max = Maximum; N = Number of participants in each treatment group; n = Number of participants who are in the corresponding category; SD = Standard deviation.

Source: Table 14.1.8.

7.2. Adverse Events

7.2.1. Brief Summary of Adverse Events

A total of 96 participants (96%) (n = 54 in the 1L population [100%] and n = 42 in the 2L population [91.3%]) experienced at least 1 treatment-emergent adverse event (TEAE) during the study. A total of 6 participants (6%) (n = 4 in the 1L population [7.4%] and n = 2 in the 2L population [4.3%]) experienced at least 1 treatment-emergent serious adverse event (SAE). A brief summary of these SAEs is included in Section 7.3.1, with safety narratives provided in Section 10.2.3.

Table 4 summarizes all adverse events across the study and Table 5 summarizes the reported TEAEs by Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term (≥5%).

Table 4 Overview of Adverse Events Prior to Treatment and Treatment-emergent Adverse Events (Safety Analysis Population)

	1L (N=54) n (%) [E]	2L (N=46) n (%) [E]	Total (N=100) n (%) [E]
Any TEAE	54 (100.0) [543]	42 (91.3) [248]	96 (96.0) [791]
Any AE Prior to Treatment	11 (20.4) [17]	12 (26.1) [21]	23 (23.0) [38]
Serious TEAE	4 (7.4) [9]	2 (4.3) [3]	6 (6.0) [12]
Serious AE Prior to Treatment	1 (1.9) [1]	1 (2.2) [1]	2 (2.0) [2]
Serious, Related TEAEs	3 (5.6) [5]	1 (2.2) [1]	4 (4.0) [6]
TEAEs Resulting in Death	1 (1.9) [1]	0	1 (1.0) [1]
Related TEAEs Resulting in Death	0	0	0
AE Prior to Treatment Leading to Drug Interruption	1 (1.9) [1]	0	1 (1.0) [1]
TEAEs Leading to Drug Interruption	10 (18.5) [19]	8 (17.4) [13]	18 (18.0) [32]
TEAEs Leading to Dose Reduction	3 (5.6) [5]	1 (2.2) [1]	4 (4.0) [6]
TEAEs Leading to Drug Discontinuation	9 (16.7) [20]	0	9 (9.0) [20]
TEAEs Leading to Any Dose Modification	3 (5.6) [5]	1 (2.2) [1]	4 (4.0) [6]
TEAEs Leading to Study Discontinuation	3 (5.6) [10]	1 (2.2) [1]	4 (4.0) [11]

Abbreviations: 1L = First-line population of newly diagnosed, treatment-naive participants with HR+/HER2- mBC; 2L = Second-line population of participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole; AE = Adverse event; E = Number of events; N = Number of participants in each treatment group; n = Number of participants who are in the corresponding category; TEAE = Treatment-emergent Adverse Event.
Percentages are calculated as (n/N)*100.
Source: Table 14.3.1.1.1 and Table 14.3.1.1.2.

7.2.2. Display of Adverse Events

Table 5 Summary of Treatment-emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term (≥ 5%) (Safety Analysis Set)

System Organ Class Preferred Term	1L (N=54) n (%) [E]	2L (N=46) n (%) [E]	Total (N=100) n (%) [E]
Any TEAE	54 (100.0) [543]	42 (91.3) [248]	96 (96.0) [791]
Investigations	30 (55.6) [134]	23 (50.0) [96]	53 (53.0) [230]
Neutrophil count decreased	16 (29.6) [41]	16 (34.8) [47]	32 (32.0) [88]
White blood cell count decreased	14 (25.9) [32]	11 (23.9) [34]	25 (25.0) [66]
Alanine aminotransferase increased	5 (9.3) [9]	3 (6.5) [4]	8 (8.0) [13]
Aspartate aminotransferase increased	4 (7.4) [5]	3 (6.5) [3]	7 (7.0) [8]
Blood creatinine increased	4 (7.4) [5]	1 (2.2) [1]	5 (5.0) [6]
Gamma-glutamyltransferase increased	4 (7.4) [11]	0	4 (4.0) [11]
Platelet count decreased	3 (5.6) [4]	1 (2.2) [3]	4 (4.0) [7]
Blood alkaline phosphatase increased	3 (5.6) [3]	0	3 (3.0) [3]
Weight decreased	3 (5.6) [5]	0	3 (3.0) [5]
Gastrointestinal disorders	31 (57.4) [81]	21 (45.7) [37]	52 (52.0) [118]
Diarrhoea	23 (42.6) [32]	12 (26.1) [14]	35 (35.0) [46]
Nausea	20 (37.0) [23]	9 (19.6) [9]	29 (29.0) [32]
Vomiting	7 (13.0) [9]	4 (8.7) [6]	11 (11.0) [15]
Constipation	4 (7.4) [4]	0	4 (4.0) [4]
Dry mouth	4 (7.4) [4]	0	4 (4.0) [4]
Blood and lymphatic system disorders	22 (40.7) [103]	15 (32.6) [28]	37 (37.0) [131]
Anaemia	14 (25.9) [25]	11 (23.9) [16]	25 (25.0) [41]
Neutropenia	12 (22.2) [44]	4 (8.7) [9]	16 (16.0) [53]
Leukopenia	6 (11.1) [17]	0	6 (6.0) [17]
Thrombocytopenia	3 (5.6) [15]	0	3 (3.0) [15]
General disorders and administration site conditions	24 (44.4) [38]	11 (23.9) [14]	35 (35.0) [52]
Fatigue	17 (31.5) [22]	8 (17.4) [8]	25 (25.0) [30]
Oedema peripheral	4 (7.4) [4]	1 (2.2) [1]	5 (5.0) [5]
Infections and infestations	19 (35.2) [39]	16 (34.8) [24]	35 (35.0) [63]
Urinary tract infection	7 (13.0) [10]	9 (19.6) [12]	16 (16.0) [22]
Upper respiratory tract infection	5 (9.3) [6]	3 (6.5) [4]	8 (8.0) [10]
COVID-19	3 (5.6) [3]	1 (2.2) [1]	4 (4.0) [4]
Metabolism and nutrition disorders	17 (31.5) [24]	6 (13.0) [9]	23 (23.0) [33]
Decreased appetite	7 (13.0) [9]	2 (4.3) [2]	9 (9.0) [11]
Hypokalaemia	7 (13.0) [7]	0	7 (7.0) [7]
Hypocalcaemia	3 (5.6) [3]	2 (4.3) [3]	5 (5.0) [6]
Musculoskeletal and connective tissue disorders	12 (22.2) [19]	7 (15.2) [7]	19 (19.0) [26]
Arthralgia	5 (9.3) [5]	2 (4.3) [2]	7 (7.0) [7]
Pain in extremity	3 (5.6) [3]	1 (2.2) [1]	4 (4.0) [4]
Back pain	3 (5.6) [4]	0	3 (3.0) [4]
Nervous system disorders	11 (20.4) [15]	6 (13.0) [7]	17 (17.0) [22]
Headache	6 (11.1) [6]	2 (4.3) [2]	8 (8.0) [8]
Dysgeusia	3 (5.6) [3]	0	3 (3.0) [3]
Skin and subcutaneous tissue disorders	13 (24.1) [20]	4 (8.7) [4]	17 (17.0) [24]
Alopecia	5 (9.3) [5]	1 (2.2) [1]	6 (6.0) [6]

System Organ Class Preferred Term	1L (N=54) n (%) [E]	2L (N=46) n (%) [E]	Total (N=100) n (%) [E]
Pruritus	3 (5.6) [3]	0	3 (3.0) [3]
Vascular disorders	8 (14.8) [12]	5 (10.9) [6]	13 (13.0) [18]
Hot flush	4 (7.4) [4]	1 (2.2) [2]	5 (5.0) [6]
Psychiatric disorders	8 (14.8) [9]	4 (8.7) [5]	12 (12.0) [14]
Insomnia	4 (7.4) [4]	2 (4.3) [2]	6 (6.0) [6]
Respiratory, thoracic and mediastinal disorders	8 (14.8) [23]	1 (2.2) [1]	9 (9.0) [24]
Dyspnoea	4 (7.4) [5]	1 (2.2) [1]	5 (5.0) [6]
Epistaxis	3 (5.6) [3]	0	3 (3.0) [3]
Ear and labyrinth disorders	4 (7.4) [5]	0	4 (4.0) [5]
Vertigo	4 (7.4) [5]	0	4 (4.0) [5]

Abbreviations: 1L = First-line population of newly diagnosed, treatment-naive participants with HR+/HER2- mBC; 2L = Second-line population of participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole; COVID-19 = Coronavirus disease-19; E = Number of events; N = Number of participants in each treatment group; n = Number of participants who are in the corresponding category; TEAE = Treatment-emergent Adverse Event.

Percentages are calculated as (n/N)*100.

Source: Table 14.3.1.2.1.

7.2.3. Analysis of Adverse Events

The most commonly reported TEAEs in the study, regardless of Investigator-assessed severity or causality, were diarrhoea (in 35 participants [35%]), neutrophil count decreased (in 32 participants [32%]), nausea (in 29 participants [29%]), and fatigue, anaemia, and white blood cell count decreased (all in 25 participants [25%]). Except for diarrhoea (42.6% vs 26.1%), nausea (37% vs 19.6%), and fatigue (31.5% vs 17.4%); there were no notable differences in the TEAEs reported in the 1L arm as compared to those in the 2L arm (Table 14.3.1.2.1).

A total of 86 participants (86%)—48 (88.9%) in the 1L arm and 38 (82.6%) in the 2L arm—were assessed by the Investigator as experiencing at least 1 TEAE related to study treatment (Table 14.3.1.5).

Note: Related causality included possibly-related, probably-related, and definitely related-TEAEs.

A total of 41 participants—23 (42.6%) in the 1L arm and 18 (39.1%) in the 2L arm—experienced at least 1 TEAE of Grade 3 or higher severity (as assessed by the Investigator per National Cancer Institute Common Terminology Criteria for Adverse Events). One participant in the 1L arm had an AE of Grade 5 severity (Table 14.3.1.4).

7.2.4. Listing of Adverse Events by Participant

A listing of TEAEs by participant is provided in Appendix 11.4.

7.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

7.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

7.3.1.1. Deaths

As presented in Table 14.3.2.12, 7 (7%) participants (4 [7.4%] in the 1L arm and 3 [6.5%] in the 2L arm) died during the study mainly due to progressive disease (3 [5.6%] participants in the 1L arm and 2 [4.3%] participants in the 2L arm). One (1.9%) participant in the 1L arm died due to AE and 1 (2.2%) participant in the 2L arm died due to unknown reason during the study.

One (1.9%) participant in the 1L arm, discontinued the study due to death. The site failed to complete the death form for the participant which led to a discrepancy between the count of death between Table 14.1.1 and Table 14.3.2.12 or Listing 16.2.7.3. Due to this discrepancy, the participant's death is not presented in Table 14.3.2.12 or Listing 16.2.7.3. A Note to File is submitted for this participant which is available in Appendix 11.2.

Brief detail of the fatal AE is as follows, with safety narratives provided in Section 10.2.3.

Overview of 1L Arm Death due to AE

- One participant had Grade 5 pneumothorax during the study. At baseline, the participant was noted with non-target lesions and measurable disease with an Eastern Cooperative Oncology Group (ECOG) performance score of 1. The event of pneumothorax was considered serious due to hospitalization and for being fatal. The administration of lerociclib was withdrawn due to the event, and the event was not considered by the Investigator related to lerociclib. The participant died 6 days after the event onset (Listing 16.2.7.1, 16.2.7.2, and 16.2.7.3).

7.3.1.2. Other Serious Adverse Events

Overall, 2 (2%) participants, 1 each in 1L and 2L arm, experienced 2 SAEs prior to receiving study intervention (Table 14.3.1.1.2). A total of 6 participants (4 [7.4%] in the 1L arm and 2 [4.3%] in the 2L arm) experienced nonfatal treatment-emergent SAEs during the study (Listing 16.2.7.1 and 16.2.7.2). Brief details of these nonfatal serious TEAEs are as follows, with narratives provided in Section 10.2.3.

Overview of 1L Arm Nonfatal Treatment-emergent SAEs

- One participant had Grade 3 pneumonitis and Grade 4 pneumothorax during the study. At baseline, the participant was noted with non-target lesions and measurable disease with an ECOG performance score of 1. The event of pneumonitis was considered serious due to hospitalization and lerociclib was interrupted due to the event. The event was considered possibly related to lerociclib and was resolved 8 days after the event onset.

  The event of pneumothorax was considered serious due to hospitalization and for being life-threatening and was considered unlikely to be related to lerociclib. No action with lerociclib administration was taken due to the event. The event was resolved 8 days after the event onset.

- One participant had Grade 4 psychotic disorder, which was considered serious due to hospitalization; and lerociclib was withdrawn due to the event. At baseline, the participant was noted with non-target lesions and no measurable disease with an ECOG performance score of 1. The event was considered unlikely to be related to lerociclib and was resolved 34 days after the event onset.
- One participant experienced Grade 3 vertigo and dehydration, which were considered serious due to hospitalization and lerociclib was withdrawn due to both the events. At baseline, the participant was noted with non-target lesions and measurable disease with an ECOG performance score of 0. The events were possibly related to lerociclib. The events of vertigo and dehydration were resolved 3 and 2 days after the events onset, respectively.
- One participant had Grade 1 pyrexia, and Grade 3 decreased appetite and bacterial sepsis. These events were considered serious due to hospitalization. At baseline, the participant was noted with non-target lesions and measurable disease with an ECOG performance score of 1. The event of pyrexia led to lerociclib administration interruption, was not related to lerociclib, and resolved 1 day after the event onset.
  The events of decreased appetite and bacterial sepsis led to lerociclib administration withdrawn and were considered probably related to lerociclib. These events were resolved 5 days after the events onset.

Overview of 2L Arm Nonfatal Treatment-emergent SAEs

- One participant had Grade 2 anaemia and Grade 3 non-cardiac chest pain. At baseline, the participant was noted with non-target lesions and measurable disease with an ECOG performance score of 1. These events were considered serious due to hospitalization and action taken with the lerociclib administration due to both the events were not applicable. The anaemia was possibly related to lerociclib and was ongoing at the time of data cutoff. The non-cardiac chest pain was not related to lerociclib and was resolved 1 day after the events onset.
- One participant had Grade 2 upper respiratory tract infection, which was considered serious due to hospitalization and for being life-threatening. At baseline, the participant was noted with non-target lesions and measurable disease with an ECOG performance score of 1. Lerociclib administration was interrupted due to the event. The event was considered not related to lerociclib and was resolved 3 days after the event onset.

7.3.1.3. Other Significant Adverse Events

In total, 9 (9%) participants experienced TEAEs leading to withdrawal of study intervention (9 [16.7%] in the 1L arm), while 4 participants (4%) experienced TEAEs leading to discontinuation from the study (3 [5.6%] in the 1L arm and 1 [2.2%] in the 2L arm) (Table 14.3.1.1.1).

The most common reasons for study intervention withdrawal were alanine aminotransferase increased, aspartate aminotransferase increased, decreased appetite, and vertigo (all, 2%), while the most common reasons for study discontinuation were alanine aminotransferase increased and aspartate aminotransferase increased (both, 2%) (Table 14.3.2.3.1).

7.4. Clinical Laboratory Evaluation

7.4.1. Listing of Individual Laboratory Measurements by Participant and Each Abnormal Laboratory Value

The following listings of individual clinical laboratory data are provided in Appendix 11.2:

- Listing 16.2.8.1.1, Laboratory Data – Hematology.
- Listing 16.2.8.1.2, Laboratory Data – Clinical Chemistry.
- Listing 16.2.8.1.3, Laboratory Data – Urinalysis.
- Listing 16.2.8.1.4, Laboratory Data – Fasting Lipid Panel.
- Listing 16.2.8.1.5, Laboratory Data – Coagulation.

7.4.1.1. Hematology

A summary of hematology laboratory values and changes from baseline over time is provided in Table 14.3.4.1.1. A shift table of hematology values comparing abnormalities from baseline to post-baseline is provided in Table 14.3.4.1.2.

No clinically significant findings were observed.

7.4.1.2. Chemistry

A summary of chemistry laboratory values and changes from baseline over time is provided in Table 14.3.4.2.1. A shift table of chemistry values comparing abnormalities from baseline to post-baseline is provided in Table 14.3.4.2.2.

No clinically significant findings were observed.

7.4.1.3. Urinalysis

A summary of abnormal urinalysis laboratory assessments is provided in Table 14.3.4.3.

No clinically significant findings were observed.

7.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

7.5.1. Vital Signs

A summary of vital signs is provided in Table 14.3.5.

No clinically significant findings were observed.

A listing of vital signs for each participant is provided in Listing 16.2.9.1.

7.5.2. Electrocardiograms

A summary of abnormal and clinically significant electrocardiograms (ECGs) is provided in Table 14.3.6.1. The ECG interpretations were summarized in Table 14.3.6.2. An analysis of ECG (QT corrected by Fridericia) abnormalities is provided in Table 14.3.6.3.

No clinically significant findings on ECG were observed.

A listing of 12-lead ECG results for each participant is provided in Listing 16.2.9.2.

7.6. Safety Conclusions

- Overall, 100 participants (n = 54 in the 1L population and n = 46 in the 2L population) were exposed to study intervention.
- A total of 6 (6%) participants experienced 12 treatment-emergent SAEs and 2 (2%) participants had 2 SAEs prior to receiving study intervention. The proportion of participants with SAEs were similar in both study populations.
- A total of 41 participants—23 (42.6%) in the 1L arm and 18 (39.1%) in the 2L arm—experienced at least 1 TEAE of Grade 3 or higher severity. One participant in the 1L arm had an AE of Grade 5 severity.
- At a SOC level, the most common TEAEs were 'Investigations' (53%), 'Gastrointestinal disorders' (52%), 'Blood and lymphatic system disorders' (37%), and 'General disorders and administration site conditions' and 'Infections and infestations' (both, 35%).
- Overall, the most common TEAEs were diarrhoea (35%), neutrophil count decreased (32%), nausea (29%), and anaemia, fatigue, and white blood cell count decreased (all, 25%). The proportion of participants reporting TEAEs were comparable between the two study populations.
- Overall, 8 (8%) participants died during the study. One (1%) participant in the 1L arm experienced a fatal SAE of pneumothorax, 5 participants (n = 3 in the 1L population and n = 2 in the 2L population) died due to progressive disease, and 1 participant in the 2L population died due to unknown cause. One (1.9%) participant in the 1L arm discontinued the study due to death. The site failed to complete the death form for the participant. A Note to File is submitted for this participant.
- A total of 86 participants (86%) had TEAEs related to study intervention. The proportion of participants reporting related-TEAEs were comparable between the two study populations.
- No clinically relevant trends were observed for any of the clinical laboratory parameters, vital signs measurements, or ECG parameters. Some values were reported outside the normal ranges; however, these were deemed as not clinically significant by the Investigator.

8. EFFICACY EVALUATION

8.1. Analysis of Efficacy

The evaluable efficacy data collected prior to the early termination of the study by the Sponsor are summarized in Table 6 and Table 7. Key findings based on the available data include the following:

- The objective response rate based on RECIST v1.1 and 95% confidence intervals (CIs) in the Response Evaluable Analysis Set was higher in 1L population (23.1% [95% CI, 11.13 to 39.33]) when compared with 2L population (11.4% [95% CI, 3.20 to 26.74]) (Table 6).
- The clinical benefit rate was higher in 1L population (79.5% [95% CI, 63.54 to 90.70]) when compared with 2L population (68.6% [95% CI, 50.71 to 83.15)]) (Table 6).
- A best response of partial response was observed in 23.1% participants in the 1L population and 11.4% participants in the 2L population and a best response of stable disease was observed in 56.4% participants in the 1L population and 57.1% participants in the 2L population (Table 6).
- The estimated progression-free survival (PFS) rate up to 6 months with 95% CI was 0.82 (57.35, 93.37) in the 1L population and 0.70 (46.72, 84.08) in the 2L population. For 12 and 18 months, the estimated PFS rate in the 1L population was same as 6 months data; however, PFS rates for 2L population were not estimable (Table 7). The median follow-up time was not reported.

Table 6 Summary of Best Overall Response, Objective Response Rate, and Clinical Benefit Rate (Response Evaluable Analysis Set)

	1L (N=39)	2L (N=35)
Best Overall Response		
CR (confirmed)	0	0
PR (confirmed)	9 (23.1)	4 (11.4)
SD	22 (56.4)	20 (57.1)
PD	4 (10.3)	8 (22.9)
NE	0	0
Non-CR/Non-PD	0	0
NED	0	0
ORR [1]	9 (23.1%)	4 (11.4%)
95% CI	(11.13%, 39.33%)	(3.20%, 26.74%)
CBR [2]	31 (79.5%)	24 (68.6%)
95% CI	(63.54%, 90.70%)	(50.71%, 83.15%)

Abbreviations: 1L = First-line population of newly diagnosed, treatment-naive participants with HR+/HER2- mBC; 2L = Second-line population of participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole; CBR = Clinical Benefit Rate; CI = Confidence interval; CR = Complete Response; ORR = Objective Response Rate; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease; NE = Not Evaluable; NED = No evidence of disease.
[1] ORR is defined as the percentage of participants achieving a confirmed CR or confirmed PR based on RECIST, v1.1.
[2] CBR is defined as the percentage of participants having achieved a confirmed CR, confirmed PR, or SD.
The 95% CIs are calculated using the Clopper-Pearson method.
Source: Table 14.2.1.1.

Table 7 Kaplan-Meier Estimates for Progression-free Survival (Full Analysis Set)

	1L (N=54)	2L (N=46)
Number of Participants [n (%)]		
Events [1]	4 (7.4)	8 (17.4)
Censored	50 (92.6)	38 (82.6)
Time to Event (days) [2]		
Q1 (95% CI)	NE (NE, NE)	64.00 (61.00, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
Q3 (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	2, 560	2, 229
Probability of Progression-free Survival (95% CI) [3]		
Up to 6 Months	0.82 (57.35, 93.37)	0.70 (46.72, 84.08)
Up to 12 Months	0.82 (57.35, 93.37)	NE (NE, NE)
Up to 18 Months	0.82 (57.35, 93.37)	NE (NE, NE)
Up to 24 Months	NE (NE, NE)	NE (NE, NE)
Up to 30 Months	NE (NE, NE)	NE (NE, NE)
Up to 36 Months	NE (NE, NE)	NE (NE, NE)
Up to 42 Months	NE (NE, NE)	NE (NE, NE)

Abbreviations: 1L = First-line population of newly diagnosed, treatment-naive participants with HR+/HER2- mBC; 2L = Second-line population of participants with HR+/HER2- mBC who have already progressed on first-line endocrine therapy such as tamoxifen, anastrozole, or letrozole; CI = Confidence interval; NE = not estimable; Q1 = first quartile; Q3 = third quartile.
[1] An event is defined as progression of disease based on RECIST, v1.1 or death.
[2] Estimates are from a Kaplan-Meier analysis.
[3] The 95% CIs are calculated using the log-log transformation.
A month is defined as 28 days or 1 cycle.
Source: Table 14.2.2.1.1.

9. DISCUSSION AND OVERALL CONCLUSIONS

9.1. Discussion

This was 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. This study was conducted 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. However, the study was closed early by the Sponsor due to corporate changes at EQRx requiring termination of all clinical activities.

9.2. Conclusions

Overall, 115 participants were screened to enroll 100 participants (n = 54 in the 1L arm and n = 46 in the 2L arm) in the study. All participants were discontinued from the study primarily due to study termination by Sponsor (83%). Overall, 96 participants experienced at least 1 TEAE during the study, the majority of the participants (55%) had AEs of Grade 1 or 2. Six participants experienced at least 1 treatment-emergent SAE, out of which one was fatal and unrelated to study intervention. Overall, 8 (8%) participants died during the study mainly due to progressive disease. Most of the participants (86%) experienced at least 1 TEAE related to study intervention, and the proportion of participants reporting related-TEAEs were comparable between the two study populations.

10. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

10.1. Disposition Data Summary Figures and Tables

Table or Figure Number	Table or Figure Title	Applicable Analysis Population
Table 14.1.4	Demographics and Other Baseline Characteristics	Safety Analysis Set

10.2. Safety Data Summary Figures and Tables

10.2.1. Displays of Adverse Events

Table or Figure Number	Table or Figure Title	Applicable Analysis Population
Table 14.3.1.1.1	Overall Summary of Treatment-emergent Adverse Events	Safety Analysis Set
Table 14.3.1.1.2	Overall Summary of Adverse Events (AEs) Prior to Treatment	Safety Analysis Set
Table 14.3.1.2.1	Summary of Treatment-emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.4	Summary of Treatment-emergent Adverse Events (TEAEs) by Severity, System Organ Class, and Preferred Term	Safety Analysis Set
Table 14.3.1.5	Summary of Treatment-emergent Adverse Events (TEAEs) by Causality, System Organ Class, and Preferred Term	Safety Analysis Set
Table 14.3.2.12	Summary of Deaths by Primary Cause of Death	Safety Analysis Set
Table 14.3.4.1.1	Summary of Hematology Laboratory Assessments	Safety Analysis Set
Table 14.3.4.1.2	Abnormal Hematology Shift from Baseline	Safety Analysis Set
Table 14.3.4.2.1	Summary of Clinical Chemistry Laboratory Assessments	Safety Analysis Set
Table 14.3.4.2.2	Abnormal Clinical Chemistry Shift from Baseline	Safety Analysis Set
Table 14.3.4.3	Summary of Abnormal Urinalysis Laboratory Assessments	Safety Analysis Set
Table 14.3.5	Summary of Vital Signs	Safety Analysis Set
Table 14.3.6.1	Summary of Abnormal and Clinically Significant ECGs	Safety Analysis Set
Table 14.3.6.2	ECG Interpretation	Safety Analysis Set
Table 14.3.6.3	Summary of ECG QT Corrected by Fridericia (QTcF) Abnormalities	Safety Analysis Set

10.2.2. Listings of Deaths, Other Serious, and Significant Adverse Events

Listing Number	Listing Title	Applicable Analysis Population
Listing 16.2.7.1	Treatment-emergent Adverse Events (TEAEs)	Safety Analysis Set
Listing 16.2.7.2	Serious Treatment-emergent Adverse Events (TEAEs)	Safety Analysis Set
Listing 16.2.7.3	All Deaths	Safety Analysis Set

10.2.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Safety narratives for deaths and other SAEs are provided immediately below.

PLACEHOLDER FOR NARRATIVES

10.2.4. Abnormal Laboratory Value Listings

Listing Number	Listing Title	Applicable Analysis Population
Listing 16.2.8.1.1	Hematology Laboratory Assessments	Safety Analysis Set
Listing 16.2.8.1.2	Clinical Chemistry Laboratory Assessments	Safety Analysis Set
Listing 16.2.8.1.3	Urinalysis Laboratory Assessments	Safety Analysis Set
Listing 16.2.8.1.4	Fasting Lipid Panel Laboratory Assessments	Safety Analysis Set
Listing 16.2.8.1.5	Coagulation Laboratory Assessments	Safety Analysis Set

10.2.5. Abnormal Vital Sign and Electrocardiogram Listings

Listing Number	Listing Title	Applicable Analysis Population
Listing 16.2.9.1	Vital Signs	Safety Analysis Set
Listing 16.2.9.2	Electrocardiograms (ECGs)	Safety Analysis Set

11. APPENDICES

11.1. Study Information

Number	Title
Appendix 11.1.1	Protocol and Amendments
Appendix 11.1.2	Sample Case Report Forms
Appendix 11.1.5	Signature of Sponsor's Responsible Medical Officer and Signature of Coordinating Investigator

11.2. Subject Data Listings (Safety Data)

Listing Number	Listing Title	Applicable Analysis Population
Listing 16.2.1.1	Participant Disposition	All participants
Listing 16.2.4.1	Demographics and Other Baseline Characteristics	All participants
Listing 16.2.4.4	Prior and Concomitant Medications	All participants
Listing 16.2.4.5	Prior and Concomitant Procedures	All participants
Listing 16.2.4.6	Subsequent Antineoplastic Cancer Therapy	All participants
Listing 16.2.6.1	Best Overall Response, Objective Response Criteria, and Clinical Benefit Criteria	All participants
Listing 16.2.7.1	Treatment-Emergent Adverse Events (TEAEs)	All participants
Listing 16.2.7.2	Serious Treatment-Emergent Adverse Events (TEAEs)	All participants
Listing 16.2.7.3	All Deaths	All participants
Listing 16.2.8.1.1	Hematology Laboratory Assessments	All participants
Listing 16.2.8.1.2	Clinical Chemistry Laboratory Assessments	All participants
Listing 16.2.8.1.3	Urinalysis Laboratory Assessments	All participants
Listing 16.2.8.1.4	Fasting Lipid Panel Laboratory Assessments	All participants
Listing 16.2.8.1.5	Coagulation Laboratory Assessments	All participants
Listing 16.2.9.1	Vital Signs	All participants
Listing 16.2.9.2	Electrocardiograms (ECGs)	All participants

11.3. Case Report Forms

11.3.1. CRFs for Deaths, Other SAEs, and Withdrawals for AEs