# A Phase 3, Randomized, Open-Label Study of Imlunestrant, Investigator*s Choice of Endocrine Therapy, and Imlunestrant plus Abemaciclib in Patients with Estrogen Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer Previously Treated with Endocrine Therapy

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This study has been transitioned to CTIS with ID 2023-506786-63-00 check the CTIS register for the current data. Main objective:•To compare the progression-free survival of imlunestrant (Arm A) to the standard comparator of Investigator's...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Breast neoplasms benign (incl nipple) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON54215

**Source**
ToetsingOnline

**Brief title**
J2J-OX-JZLC / EMBER-3

### Condition

- Breast neoplasms benign (incl nipple)

**Synonym**
Locally Advanced or Metastatic Breast Cancer; Breast Cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Eli Lilly
**Source(s) of monetary or material Support:** Eli Lilly and Company

## Intervention

**Keyword:** Breast Cancer, Estrogen Receptor Positive, HER2 Negative, oral SERD

## Outcome measures

### Primary outcome

1.Progression Free Survival (PFS) by investigator assessment

• Investigator-assessed PFS (between Arm A and Arm B) in the ITT population

• Investigator-assessed PFS (between Arm A and Arm B) in the ESR1- mutation

detected population

• Investigator-assessed PFS (between Arm C and Arm A) in the ITT population

### Secondary outcome

2. Overall Survival (OS)

3. Objective Response Rate (ORR): Percentage of Participants Who Achieve a

Confirmed Best Overall Response of Complete Response (CR)

or Partial Response (PR)

4. Duration of Response (DoR)

5. Clinical Benefit Rate (CBR): Percentage of Participants Who Achieve a Best

Overall Response of CR, PR or Stable Disease for greater than or equal to (>=)

24 weeks

6. Progression Free Survival (PFS) by blinded independent review

7. Patient Reported Outcomes (PRO): Time to Worsening of "Worst Pain" Measured by the Worst Pain Numeric Rating Scale (NRS). NRS is a single item, participant-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "pain as bad as you can imagine."

8. Pharmacokinetics (PK): Steady State Plasma Concentrations of Imlunestrant

9.Pharmacokinetics (PK): Steady State Plasma Concentrations of Imlunestrant and Abemaciclib

# Study description

**Background summary**

There remains an unmet medical need for novel, improved, and tolerable ETs for the management of ER+, HER2- mBC, that can overcome the PK and resistance limitations of ETs currently used in the clinic. To this end, promising clinical data have been observed with the oral SERD, imlunestrant, in heavily pretreated ER+ mBC patients. Along with this, abemaciclib has well established clinical benefit in CDK4/6-naïve patients in the 1st and 2nd line setting and has the potential for benefit in CDK4/6-pre-treated patients . The clinical and the preclinical results outlined in Section 2.1 support further investigation of imlunestrant and imlunestrant plus abemaciclib for patients with ER+, HER2- locally advanced or mBC.The purpose of this study, in patients with ER+, HER2- locally advanced or mBC previously treated with an AI with or without a CDK4/6 inhibitor, is to determine whether: imlunestrant prolongs PFS compared to Investigator*s Choice of Endocrine Therapy; and if imlunestrant plus abemaciclib prolongs PFS compared to imlunestrant monotherapy.Patient randomization within this study will be stratified by known prognostic factors to reduce the potential for bias and improve the power of the analyses. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes

bias in the assessment and interpretation of observed treatment effects.

## Study objective

This study has been transitioned to CTIS with ID 2023-506786-63-00 check the CTIS register for the current data.

Main objective:
•To compare the progression-free survival of imlunestrant (Arm A) to the standard comparator of Investigator's Choice Endocrine Therapy of either fulvestrant or exemestane (Arm B) in the ITT population
•To compare the PFS of Arm A to Arm B in the ESR1-mutation detected population
•To compare the progression-free survival of imlunestrant plus abemaciclib (Arm C) to imlunestrant (Arm A) in the ITT population

Secondary objectives:
•To compare OS of Arm A to Arm B in the ITT population
•To compare OS of Arm A to Arm B in the ESR1-mutation detected population
•To compare OS of Arm C to Arm A in the ITT population
•To assess the safety and tolerability of each treatment arm
•To evaluate the effectiveness of Arm A compared to Arm B and Arm C compared to Arm A based on PROs of pain using the Worst Pain NRS
•To assess the PK of imlunestrant (Arm A and Arm C)
•To assess the PK of abemaciclib and its metabolites (Arm C)

## Study design

Participants will be randomized 1:1:1 between 3 treatment arms (Arm A: Arm B: Arm C) and will be treated until disease progression or other discontinuation criteria are met
* Arm A: Imlunestrant 400 mg orally QD on Days 1 to 28 of a 28-day cycle
* Arm B:Investigator*s Choice Endocrine Therapy
o Exemestane 25 mg orally QD on Days 1 to 28 of a 28-day cycle OR
o Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and beyond
* Arm C: Imlunestrant + Abemaciclib
o Imlunestrant 400 mg orally QD on Days 1 to 28 of a 28-day cycle
o Abemaciclib 150 mg orally BID on Days 1 to 28 of a 28-day cycle

## Intervention

Imlunestrant will be administered orally, 400 mg QD on Days 1 to 28 on a 28-day cycle. The imlunestrant doses will be administered at approximately the same times on each day. Patients should follow the fasting guidance provided in the patient diary.
The Investigator*s Choice of Endocrine Therapy will be limited to fulvestrant

or exemestane.
Fulvestrant will be administered 500 mg intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250 mg injections, one in each buttock on Days 1 and 15 of Cycle 1 of a 28-day cycle, then on Day 1 of Cycle 2 and beyond. However, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.
Exemestane will be supplied as 25 mg and administered orally, 25 mg QD.
Abemaciclib will be administered orally, 150 mg BID on Days 1 to 28 on a 28-day cycle. The abemaciclib doses will be administered at approximately the same times on each day

**Study burden and risks**

Imlunestrant toxicology studies demonstrate an acceptable safety profile, with toxicities that are generally monitorable and/or reversible and are clinically manageable in the EMBER-3 patient population.

Although the study procedures are generally consistent with standard of care, increased monitoring of vital signs(including blood pressure), haematology, hepatic panels, and electrocardiograms (ECGs) occur in the initial cycles to monitor for potential toxicities of interest.
Additionally, a data monitoring committee (DMC) will assess unblinded safety data during the trial on a regular basis. The DMC will evaluate all safety-related data provided for each meeting to determine whether a change in the conduct of the trial is warranted for the safety of patients.

Given the high unmet need for additional therapies to treat ER+, HER2- locally advanced or mBC, the clinical safety profile of imlunestrant, and the clinical efficacy observed in patients in other studies, the risk/benefit assessment supports evaluation of imlunestrant in the proposed patient population.

# Contacts

**Public**
Eli Lilly

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**Scientific**

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

* Have a diagnosis of ER+, HER2- locally advanced or metastatic breast cancer
* Have disease that has demonstrated progression on or after an aromatase inhibitor alone or in combination with a CDK4/6 inhibitor.
oPatients are expected to have received prior treatment with a CDK4/6 inhibitor if this treatment is approved and can be reimbursed
* Must be deemed appropriate for treatment with endocrine therapy
* If female, have a postmenopausal status by natural or surgical means or by ovarian function suppression
* Have RECIST evaluable disease (measurable disease and/or nonmeasurable bone-only disease)
* Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale (Oken et al. 1982)
* Have adequate renal, hematologic, and hepatic organ function

## Exclusion criteria

* Have received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant, or any investigational-ER-directed therapy (including SERDs and non-SERDs), any PI3K-, mTOR- or AKT- inhibitor
* Have visceral crisis, lymphangitic spread within the lung, or any evidence of leptomeningeal disease.

* Have symptomatic or untreated brain metastasis.
* Have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study
* Known allergic reaction against any of the components of the study treatment

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 06-09-2022 |
| Enrollment: | 18 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Exemestane |
| Generic name: | Exemestane |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Fulvestrant |
| Generic name: | Fulvestrant |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |

| | |
|---|---|
| Brand name: | Imlunestrant |
| Generic name: | LY3484356 |
| Product type: | Medicine |
| Brand name: | Verzenios |
| Generic name: | LY2835219 / Abemaciclib |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 05-04-2022 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-07-2022 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 24-07-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-08-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 11-10-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 02-11-2022 |

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|---|---|
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 05-02-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 09-05-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 23-06-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 10-07-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 04-10-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EU-CTR | CTIS2023-506786-63-00 |
| EudraCT | EUCTR2021-000079-35-NL |
| CCMO | NL77553.056.22 |