A Phase 1/2 Dose Escalation and Expansion Study of OP-1250 in Adults with Advanced and/or Metastatic Hormone Receptor-positive (HR+), HER2-negative (HER2-) Breast Cancer (NCT04505826)

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I will discuss the following investigational product in my presentation: OP-1250
OP-1250, a Complete Estrogen Receptor ANtagonist (CERAN)

OP-1250 potently and completely inactivates the Estrogen Receptor (ER), blocks ER-driven transcriptional activity, inhibits ER-driven breast cancer cell growth, and strongly induces degradation of ER.


AF1: activation factor 1
AF2: activation factor 2

Background and Rationale

- Estrogen receptor (ER) is a key therapeutic target for ER+/HER2-metastatic breast cancer (MBC)
- Despite the effectiveness of available endocrine therapies, most patients will ultimately develop endocrine-resistant disease. More effective and less toxic therapies are needed
- OP-1250, a CERAN (Complete Estrogen Antagonist) has demonstrated preclinically:
  - Complete ER antagonism with blockade of AF1 and AF2 transcriptional activation domains
  - Robust anti-tumor efficacy in multiple preclinical models, including in wildtype, ESR1 and PI3KA mutations
    - In nonclinical studies, OP-1250 reduced tumor size while fulvestrant only slowed tumor growth
  - Strong degradation of ERα across all tested cell lines
  - High oral bioavailability and favorable pharmacokinetic (PK) exposure, with steady-state plasma levels supporting convenient, once-daily oral dosing
  - CNS penetration, with promising nonclinical data in treating brain metastases
OP-1250 Demonstrated Robust Tumor Shrinkage Across Multiple Xenograft Models

HCC1500 (ESR1 wild-type)

ST941 (ESR1\textsuperscript{Y537S})

OP-1250 Prolonged Survival Impact in ER+ MBC Brain Metastases Model

OP-1250 was superior in shrinking ER+ tumors compared to other endocrine therapies tested, including fulvestrant and tamoxifen.

• Dosing stopped in OP-1250 10 mg/kg group at 100 days

• OP-1250 prevented death in all animals at day 120. Data suggest that OP-1250 may be an active treatment for patients with brain metastasis from ER+ breast cancer.

OP-1250 is Orally Bioavailable with Attractive Steady-State Plasma Levels

- Minimal peak-to-trough variation at steady state in 3 different species
- Steady-state plasma levels relatively constant through 24-hour period
- Profile consistent with daily oral dosing in humans

OP-1250-001: First in Human Phase I/II Clinical Study
OP-1250 oral, once-daily dosing

Phase Ia Dose Escalation
- Dose 1: 300 mg
- Dose 2: 210 mg
- Dose 3: 120 mg
- Dose 4: 60 mg
- Dose 5: 30 mg

Phase Ib Dose Expansion
- Dose 1
- Dose 2
- RP2D

Phase II Cohorts
- Cohort A
- Cohort B
- Cohort C

- Rolling 6 design
- Intermediate dosing to evaluate smaller step-ups in targeted dose range

- 1 or 2 dose cohorts, each N=15
- Patients with measurable disease
- Allows for further evaluation of 2 potential candidate Recommended Phase II Dose (RP2D)
- Findings will inform selection of RP2D

- Cohort A, B, and C
- Patients with measurable disease (N=50)
- Patients with non-measurable disease (N=15)
- Patients with CNS metastasis (N=15)
OP-1250-001: Objectives

- Open-label, Phase I/II clinical trial designed to evaluate OP-1250, administered orally once-daily in patients with ER+/HER2- recurrent, locally advanced or MBC who have had prior endocrine therapy

### Study Objectives

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<tr>
<th>Phase</th>
<th>Primary Objectives</th>
<th>Secondary and Exploratory Objectives</th>
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| Phase Ia, **Dose Escalation** | ▪ Pharmacokinetics  
▪ Safety and tolerability  
▪ Identify RP2D | ▪ Anti-tumor efficacy  
▪ Biomarker expression  
▪ ESR1 in circulating tumor DNA (ctDNA) |
| Phase Ib, **Dose Expansion** | ▪ Anti-tumor activity in measurable disease cohort  
▪ Safety and tolerability at RP2D | ▪ Clinical benefit in non-measurable disease and CNS metastasis  
▪ ctDNA for mutESR1  
▪ ER, PR and Ki67 in archival and serial biopsies |
Key Inclusion Criteria

- Adults with ER+/HER2- recurrent, locally advanced or MBC
- At least 1 prior hormonal regimen for locally advanced or metastatic disease

### Additional Criteria by Phase

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<th>Type</th>
<th>Criteria</th>
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| Ia, Dose Escalation | | ≤ 2 prior chemotherapy regimens for locally advanced or metastatic disease  
| | | Evaluable disease (measurable and non-measurable disease are eligible) |
| Ib, Dose Expansion | | Measurable disease by RECIST 1.1 criteria  
| | | ≤ 1 prior chemotherapy regimen for locally advanced or metastatic disease  
| | | ≤ 4 prior endocrine-based therapies for locally advanced or metastatic disease |
| II, Expansion | Cohort A: | Measurable disease |
| | Cohort B: | Non-measurable |
| | Cohort C: | CNS disease  
| | | ≤ 3 prior chemotherapy regimens for locally advanced or metastatic disease  
| | | Evaluable disease |
Summary

▪ OP-1250, a novel CERAN (Complete Estrogen Receptor Antagonist), has the potential to be a best-in-class endocrine therapy

▪ OP-1250 is currently in being studied in a Phase I/II First-in-Human Clinical Trial in patients with ER+/HER2-metastatic breast cancer

▪ The key objectives of the study are to assess:
  • Safety, pharmacokinetics and identification of a RP2D
  • Preliminary efficacy
  • Serial evaluation of ESR1 and other relevant genetic mutations in ctDNA

▪ The Phase Ia OP-1250-001 dose escalation, utilizing a rolling 6 design and allowing for intermediate dose levels, will be highly informative across multiple dose levels within the predicted targeted range for a RP2D

▪ Preliminary efficacy will be obtained across 3 Phase II patient cohorts (patients with measurable disease, patients with non-measurable disease, and patients with CNS metastasis), reflective of an ER+/HER2-metastatic breast cancer population

▪ Initial data from the Phase Ia dose-escalation stage anticipated in Q4 2021

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