**POPULATION PHARMACOKINETIC AND EXPRESSION-RESPONSE MODELING OF THE ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER RINTODESTRANT (G1T48) IN PATIENTS WITH ER+/HER2- ADVANCED BREAST CANCER**

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**BACKGROUND**

Rintodestrant is an orally bioavailable, potent, and selective estrogen receptor degrader (SERD) that competitively binds to the estrogen receptor (ER) and blocks ER signaling in cancer cells related to other breast cancers. To our knowledge, rintodestrant is the first orally administered estrogen receptor degrader to demonstrate beneficial effects in patients with ER+/HER2- advanced breast cancer.

**METHODS**

**Study Design**

The phase 1/2 study was a single-arm, open-label, multicenter study (NCT03455270) that included 95 pretreated patients (75%) with a ≥1 hormone receptor-positive, locally advanced, and/or metastatic breast cancer who had progressed on endocrine therapy (NCT03455270).

**Objectives**

The study was designed to evaluate the safety, tolerability, efficacy, and pharmacokinetics of rintodestrant in pretreated patients with advanced breast cancer. The primary objective of the phase 1 study was to determine the maximum tolerated dose (MTD) of rintodestrant in these patients.

**Results**

- **Efficacy**
  - At the dose of 200 mg, rintodestrant showed a favorable safety profile with limited grade ≥ 3 adverse events in the majority of patients.
  - **Objective response rate (ORR)**: 10.4% (95% CI, 4.6–19.6%)
  - **Progression-free survival (PFS)**: 15.4 months
  - **Overall response rate (ORR)**: 10.4% (95% CI, 4.6–19.6%)
  - **Disease control rate (DCR)**: 49.1% (95% CI, 38.5–59.7%)

- **Pharmacokinetics**
  - The simulated trough concentration of rintodestrant at the 800 mg recommended phase 2 dose was greater than the PD60 and PD80 Ki67 levels in most patients, indicating that the selected dose was sufficient to achieve a pharmacologically active exposure, supporting 800 mg as the PD24.

- **Conclusion**
  - Rintodestrant was well tolerated at dose levels up to and including 2000 mg/day, with prominent grade ≥ 3 adverse events primarily classified as gastrointestinal disorders. The phase 1 study dose of 200 mg was recommended for further evaluation in the phase 2 study. The trial was registered with the U.S. National Institutes of Health (NCT03455270) and is in accordance with the principles of good clinical practice and the Declaration of Helsinki. Patient consent was obtained both orally and in writing for the study. All data reported were collected as part of the approved clinical trial protocol.

**CONCLUSIONS**

- Rintodestrant was well tolerated at dose levels up to and including 2000 mg/day, with prominent grade ≥ 3 adverse events primarily classified as gastrointestinal disorders.
- The phase 1 study dose of 200 mg was recommended for further evaluation in the phase 2 study.
- The trial was registered with the U.S. National Institutes of Health (NCT03455270) and is in accordance with the principles of good clinical practice and the Declaration of Helsinki.
- Patient consent was obtained both orally and in writing for the study.
- All data reported were collected as part of the approved clinical trial protocol.

**Table 1: Summary of Ovarian PK and ER- Degradation Data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
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<tbody>
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<td>PK</td>
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<tr>
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<tr>
<td></td>
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<td>ER-Degradation</td>
<td>ER</td>
<td>Expression</td>
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**Figure 1: Schematic Diagram of the PK Model**

- The model was validated using external independent dataset from the human translational study.
- The model was developed using NONMEM, Perl-PEAK, and R to estimate drug exposure and efficacy relationships.

**Figure 2: Simulation of PK Model**

- The simulation was performed using the validated model to predict drug exposure and efficacy at different dose levels.

**Figure 3A** Extrinsic ER modulation (PD) EST (solid blue line) and ER degradation analysis (gray line) in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 3B** ER degradation analysis in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 4A** Simulation of ER modulation (PD) EST (solid blue line) and ER degradation analysis (gray line) in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 4B** ER degradation analysis in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 5A** Simulation of ER modulation (PD) EST (solid blue line) and ER degradation analysis (gray line) in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 5B** ER degradation analysis in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 6A** Simulation of ER modulation (PD) EST (solid blue line) and ER degradation analysis (gray line) in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 6B** ER degradation analysis in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 7A** Simulation of ER modulation (PD) EST (solid blue line) and ER degradation analysis (gray line) in 10 patients with ER+/HER2- metastatic breast cancer.

**Figure 7B** ER degradation analysis in 10 patients with ER+/HER2- metastatic breast cancer.