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Introduction
OP-1250: Best-in-Class Potential for ER+ / HER2- Breast Cancer

Highly Attractive Pharmacokinetic Profile
- Orally-bioavailable with long half-life, providing PK profile with low intra-day variability
- Enables complete antagonism of the estrogen receptor without the need for higher daily doses

Favorable Tolerability Profile in Heavily Pretreated Patient Population
- Phase 1 patient enrollment with significant prior CDK4/6i, chemotherapy and fulvestrant treatment
- Generally well-tolerated with no dose-limiting toxicities and maximum tolerated dose not reached

Robust Anti-Tumor Activity Demonstrated with Long Duration of Patient Benefit
- 3 partial responses in patients with ESR1 mutations (2 confirmed, 1 unconfirmed)
- Overall Response Rate of 17% (2/12) and Clinical Benefit Rate of 46% (6/13) in targeted RP2D range
- Robust target lesion reduction and duration of therapy extending beyond 1 year

Rapidly Advancing Clinical Development Program
- Phase 1a successfully completed; Efficacy data continuing to mature
- Dose expansion ongoing with Phase 2 cohorts and first CDK4/6i combination study to initiate in Q1 2022
- Expect to enroll 100+ additional patients across development program in 2022

CDK4/6i: cyclin-dependent kinases inhibitor

Olema
OP-1250: Designed to Address Unmet Need in Patients with Advanced ER+/HER2- Breast Cancer
ER+ Breast Cancer — A Significant Unmet Need

APPARENTLY

282K WOMEN
in the U.S. will be
diagnosed with breast
cancer in 2021

OVER

43,600 WOMEN
in the U.S. will die
from metastatic breast
cancer in 2021

It's Estimated That Breast Cancer Accounts for 30% of New Cancer Diagnoses in U.S. Women

Majority of All Breast Cancers express Estrogen Receptor (ER+)

- 73% HR+/HER2-
- 12% HR-/HER2-
- 11% HR+/HER2+
- 4% HR-/HER2+

Approximate $10B Market for endocrine therapies and targeted agents for ER+ breast cancer

References: American Cancer Society. Facts and Figures 2021; SEER database
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.

**References:**

AF1: activation factor 1  
AF2: activation factor 2

OP-1250: Non-Clinical Data Summary

**Complete Antagonism of ER:**
Activity in both wild-type and mutant ESR1 models by turning-off both AF1 and AF2 transcriptional activation domains

**Robust Tumor Shrinkage:**
Superiority vs. fulvestrant in head-to-head nonclinical studies

**CNS Penetration:**
Robust activity in nonclinical brain metastases studies

**Combination Therapy:**
Demonstrated additive effects in nonclinical models with other targeted agents

**Strong Degradation of ERα:**
Across all tested ER+ cell lines

**Attractive PK Profile:**
Orally bioavailable and attractive steady-state plasma levels

OP-1250 has the potential to become best-in-class endocrine therapy of choice for ER+ breast cancer
First-in-Human Phase 1/2 Clinical Study Design

OP-1250 oral, once-daily dosing

**Phase 1a Dose Escalation**
- 300 mg
- 210 mg
- 120 mg
- 90 mg
- 60 mg
- 30 mg

**Phase 1b Dose Expansion**
- 60 mg (n=15)
- 120 mg (n=15)

**Phase 2 Cohorts**
- Patients with measurable disease (N=50)
- Patients with non-measurable disease (N=15)
- Patients with CNS metastasis (N=15)

**Objectives:**
- Antitumor activity in measurable disease cohort; safety and tolerability at RP2D

**Phase 1a Key Inclusion Criteria:**
- ER+/HER2- advanced breast cancer
- ≥1 prior endocrine therapy for advanced breast cancer
- ≤2 prior chemotherapy regimens for locally advanced or metastatic disease

**Primary objectives:**
- Pharmacokinetics, safety and tolerability, identify RP2D

**Secondary objectives:**
- ORR (CR + PR);
- CBR (CR + PR + SD ≥24 weeks)
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=41 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (years)</strong></td>
<td>63</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (41)</td>
</tr>
<tr>
<td>1</td>
<td>24 (59)</td>
</tr>
<tr>
<td><strong>Measurable disease at baseline</strong></td>
<td>31 (76)</td>
</tr>
<tr>
<td><strong>Visceral disease (liver, lung, peritoneum, pleura, ascites)</strong></td>
<td>25 (61)</td>
</tr>
<tr>
<td><strong>Prior lines of therapy in advanced settings</strong></td>
<td>Median=3</td>
</tr>
<tr>
<td>(Range 1-8)</td>
<td></td>
</tr>
<tr>
<td><strong>Prior lines of endocrine therapy in advanced settings†</strong></td>
<td>Median=2</td>
</tr>
<tr>
<td>1</td>
<td>12 (29)</td>
</tr>
<tr>
<td>2</td>
<td>13 (32)</td>
</tr>
<tr>
<td>3 or more</td>
<td>15 (37)</td>
</tr>
<tr>
<td><strong>Types of prior therapies in advanced settings</strong></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>17 (42)</td>
</tr>
<tr>
<td>Aromatase inhibitor (AI)</td>
<td>31 (76)</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>28 (68)</td>
</tr>
<tr>
<td>CDK 4/6 inhibitor</td>
<td>39 (95)</td>
</tr>
<tr>
<td><strong>ESR1 mutations at baseline (ctDNA), n=39 evaluated</strong></td>
<td>19 (49)</td>
</tr>
</tbody>
</table>

*Sums may not total to 100% due to rounding  †One patient had missing data  ‡Nine patients received 2 prior CDK4/6i regimens  §ctDNA was not collected in 2 patients.  ECOG, Eastern Cooperative Oncology Group; CDK4/6, cyclin-dependent kinases.
Dose-Proportional PK with Attractive Steady-State Plasma Concentrations

- High oral bioavailability and steady-state plasma levels with minimal peak-to-trough variability
- Doses ≥60 mg QD exceed predicted efficacy thresholds
- Enables complete antagonism of the estrogen receptor without the need for higher daily doses
- Effective half life ($T_{1/2}$)=51-73 hours, supporting once-daily dosing
### Favorable Tolerability Profile

<table>
<thead>
<tr>
<th>TRAEs in ≥15% of Patients</th>
<th>30 mg (n=5)</th>
<th>60 mg (n=6)</th>
<th>90 mg (n=6)</th>
<th>120 mg (n=6)</th>
<th>150 mg (n=4)</th>
<th>210 mg (n=7)</th>
<th>300 mg (n=7)</th>
<th>Total N=41 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>G≥3</td>
<td>All</td>
<td>G≥3</td>
<td>All</td>
<td>G≥3</td>
<td>All</td>
<td>G≥3</td>
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<tr>
<td>Patients with ≥1 event</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- Adverse events primarily grade 1 or 2 across all dose levels
- No dose limiting toxicities and maximum tolerated dose not reached
- No clinically significant bradycardia, ocular toxicity or diarrhea

**Targeted RP2D range of 60 to 120 mg based on pharmacokinetics, favorable tolerability, and initial efficacy**

*As of data cut-off of November 1, 2021, 3 patients had grade 4 neutropenia attributed to study drug by the investigator that did not reach ≥15%. Two of these patients presented with fever and neutropenia. TRAE, treatment-related adverse event as assessed by study investigator.
OP-1250 Demonstrated Meaningful Anti-Tumor Activity

Best Response of Target Lesion in Patients with Measurable Disease (N=22)

Robust target lesion reduction up to 100% observed in response-eligible patients

*Patient’s response unconfirmed due to progression with a new non-target lesion at follow-up visit.

Efficacy-evaluable patients include those with measurable disease at baseline and at least one post-baseline scan. Data cut-off: November 1, 2021.

CDK4/6i, cyclin-dependent kinases inhibitor; AI, aromatase inhibitor.
Case Study 1: Confirmed Partial Response in Late-Line Patient with Peritoneal Carcinomatosis and Bone Metastasis; Lymph Node Lesion Normalized and Resolution of Peritoneal Stranding and Ascites

41-year-old female
120 mg OP-1250 QD
Confirmed Partial Response Maintained ≥9 months

Prior Therapy in Advanced / Metastatic Setting

CDK4/6i:
• Palbociclib

Endocrine Therapies:
• Aromatase inhibitors: Anastrozole
• Leuprolide
• Tamoxifen
• Fulvestrant

Chemotherapy:
• ACT
• Capecitabine

ESR1 Mutation

Y537S

71% reduction in target lesions

Responses evaluated per RECIST version 1.1. CDK4/6, cyclin-dependent kinases.
Case Study 2: Confirmed Partial Response in Late-Line Patient with Multiple Liver Metastasis

61-year-old female
60 mg OP-1250 QD
Confirmed Partial Response Maintained ≥8 months

Prior Therapy in Advanced / Metastatic Setting

CDK4/6i:
- Ribociclib

Endocrine Therapies:
- Aromatase Inhibitors:
  - Letrozole, Anastrozole, Exemestane
- Tamoxifen
- Fulvestrant

Other Targeted Agents:
- mTOR inhibitors: Everolimus

ESR1 Mutation

Y537S

Responses evaluated per RECIST version 1.1. CDK4/6, cyclin-dependent kinases; mTOR, mechanistic target of rapamycin.

46% reduction in target lesions
Durable Clinical Benefit Observed in Heavily Pretreated Population

*Four patients in the 300 mg cohort dose reduced, 3 to 120 mg and 1 to 60 mg with most occurring at the beginning of cycle 2. These patients were included in RP2D CBR calculation. CBR defined as SD persisting ≥24 weeks, or a best response of confirmed CR or PR. ORR includes patients with measurable disease only. AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinases inhibitor.

- Across dose levels:
  - ORR: 8% (2/24) , CBR: 29% (7/24)
- RP2D range (60-120 mg):
  - ORR: 17% (2/12), CBR: 46% (6/13)
- 2 confirmed partial responses (cPR) maintained ≥8 months; both patients remain on treatment
- 1 patient had 100% target lesion reduction on 30 mg OP-1250; response remained unconfirmed due to PD with new lesion identification at a follow-up visit
- Long duration of benefit, with 8 patients on therapy ≥6 months and 2 ≥1 year
- 32% of patients (13/41) still on treatment, with data maturing

*Treatment Duration (weeks) and Response by Dose in All Patients (N=41) as of Nov. 1, 2021

*Four patients in the 300 mg cohort dose reduced, 3 to 120 mg and 1 to 60 mg with most occurring at the beginning of cycle 2. These patients were included in RP2D CBR calculation. CBR defined as SD persisting ≥24 weeks, or a best response of confirmed CR or PR. ORR includes patients with measurable disease only. AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinases inhibitor.
Thank You to Our Patients and Clinical Investigators!

On Behalf of the Entire Olema Team
Perspectives and Next Steps
### Promising Early Profile with Heavily Pretreated Patients vs. Phase 1 SERDs

<table>
<thead>
<tr>
<th>Drug Candidate</th>
<th>Phase 1 Study Start</th>
<th>Median Prior Lines of Therapy in Advanced Setting</th>
<th>Percent of Patients with Prior CDK4/6i</th>
<th>Percent of Patients with Prior Fulvestrant</th>
<th>Percent of Patients with Prior Chemotherapy</th>
<th>Overall Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP-1250 Overall</td>
<td>2020</td>
<td>3</td>
<td>95%</td>
<td>68%</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>OP-1250 RP2D Range</td>
<td></td>
<td></td>
<td>94%</td>
<td>67%</td>
<td>56%</td>
<td>17%</td>
</tr>
<tr>
<td>ARV-471</td>
<td>2019</td>
<td>5</td>
<td>100%</td>
<td>71%</td>
<td>38%</td>
<td>7%</td>
</tr>
<tr>
<td>LY3484356</td>
<td>2019</td>
<td>2</td>
<td>83%</td>
<td>60%</td>
<td>26%</td>
<td>6%</td>
</tr>
<tr>
<td>rintodestrant</td>
<td>2018</td>
<td>3</td>
<td>77%</td>
<td>85%</td>
<td>50%</td>
<td>5%</td>
</tr>
<tr>
<td>ZN-c5</td>
<td>2018</td>
<td>2</td>
<td>68%</td>
<td>46%</td>
<td>NR</td>
<td>5%</td>
</tr>
<tr>
<td>camizestrant</td>
<td>2018</td>
<td>3</td>
<td>62%</td>
<td>53%</td>
<td>NR</td>
<td>10%</td>
</tr>
<tr>
<td>amcenestrant</td>
<td>2017</td>
<td>2</td>
<td>63%</td>
<td>47%</td>
<td>42%</td>
<td>7%</td>
</tr>
<tr>
<td>giredestrant</td>
<td>2017</td>
<td>1</td>
<td>59%</td>
<td>38%</td>
<td>NR</td>
<td>11%</td>
</tr>
</tbody>
</table>

NR, not reported

OP-1250: Successful Phase 1 with Key Objectives Achieved

### Highly Attractive Pharmacokinetics
- High oral bioavailability
- Dose proportional PK with exposures supporting once-daily dosing
  - Smooth profile with minimal peak-to-trough variability
- Effective half-life of 51-73 hours
- Doses ≥60 mg QD exceed predicted efficacy thresholds
  - Enables complete antagonism of ER without the need for higher daily doses

### Favorable Tolerability
- Generally well tolerated
- Adverse events were mostly Grade 1 or 2 at all dose levels
- No DLTs observed and MTD not reached
- No clinically significant bradycardia, ocular toxicity, or diarrhea
- RP2D range of 60 to 120 mg identified based on favorable pharmacokinetics, tolerability, and initial efficacy

### Promising Anti-Tumor Efficacy
- Clear efficacy signals observed in heavily pretreated patients
- 3 partial responses observed in patients with ESR1 mutations*
  - 2 confirmed and 1 unconfirmed
  - Durable cPRs ≥8months
- RP2D range (60-120 mg):
  - ORR: 17% (2/12), CBR: 46% (6/13)
- Robust target lesion reductions ≥30% observed in 4 response-eligible patients
- 13 of 41 (32%) patients remain on study; Efficacy data continues to mature

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*Best overall response as of data cutoff date of November 1, 2021

Potential best-in-class backbone endocrine therapy of choice for ER+ breast cancer
Rapidly Advancing Development Program to Support Broad Profile for OP-1250

Anticipated milestones

Q4 2021
- Complete Phase 1a dose escalation
- Initiate Phase 1b dose expansion at 60 mg and 120 mg dose levels (N=15 each)

Q1 2022
- Select RP2D
- Initiate Phase 2 cohorts
  - Measurable disease (N=50)
  - Non-measurable disease (N=15)
  - CNS metastasis (N=15)
- Initiate 1st Phase 1b CDK4/6i combination study

2H 2022
- Initiate additional Phase 1b studies in combination with CDK4/6 and PI3Kα inhibitors
- Initiate Phase 1b HER2+ study

2023
- Initiate pivotal study

2022: Present updated monotherapy and combination data

Continuing to build evidence supporting OP-1250 as a differentiated, best-in-class CERAN