Preliminary Data From a Phase 1/2, Multicenter, Dose Escalation Study of OP-1250, an Oral CERAN/SERD, in Patients With Advanced and/or Metastatic Estrogen Receptor (ER)-Positive, HER2-Negative Breast Cancer

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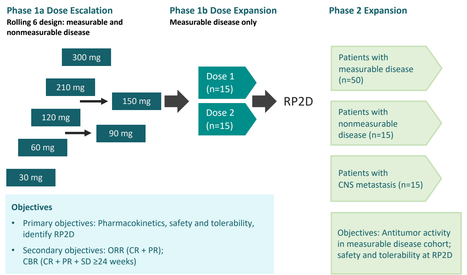
Background

- Endocrine therapy is the backbone of treatment for ER+/HER2– locally advanced or metastatic breast cancer (MBC), but more effective and tolerable options are needed as most patients develop resistance to available therapies[1,2]
- OP-1250 is a once-daily oral CERAN (complete estrogen receptor antagonist) that has demonstrated anti-tumor efficacy in a range of preclinical xenograft models of breast cancer, including in *ESR1* and *PIK3CA* mutations and central nervous system (CNS) metastasis[3,4]
- Here we present initial results from the phase 1a dose escalation of a phase 1/2 study of OP-1250 monotherapy in ER+/HER2– MBC

Methods

- OP-1250-001 (NCT04505826) is a first-in-human, phase 1/2 study of once-daily oral OP-1250 in adults with ER+/HER2– MBC (**Figure 1**)

Figure 1. OP-1250-001 Trial Design



CBR, clinical benefit rate; CNS, central nervous system; CR, complete response; ORR, overall response rate; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease.

- All patients must be adults with ER+/HER2- recurrent, locally advanced or MBC with at least 1 prior hormonal regimen for metastatic disease (**Table 1**)

Table 1. Key Inclusion Criteria for Phase 1

Phase	Inclusion Criteria
Phase 1a, dose escalation	• ≤2 prior chemotherapy regimens for locally advanced or metastatic disease • Evaluable disease (measurable and non-measurable disease are eligible)
Phase 1b, 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

RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

References

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Results

Patient Population

- Data cut-off date for this analysis was October 1, 2021
- A total of 40 patients were treated between August 2020 and October 2021
- Thirty-eight patients were postmenopausal women, 1 patient was pre/perimenopausal, and 1 patient was male. Thirty-five patients were white, 1 was African American, and 4 did not report race (**Table 2**)
- Of 40 patients, 16 were still on treatment at the time of data cut-off, and 17 had discontinued OP-1250 due to progressive disease (**Table 3**)

Table 2. Demographics and Baseline Disease Characteristics

Characteristic	30 mg (n=5)	60 mg (n=6)	90 mg (n=6)	120 mg (n=6)	150 mg (n=3)	210 mg (n=7)	300 mg (n=7)	Total (N=40)
Age (years), median	63	65	57	63	76	65	64	62
Range	54–72	34–79	40–58	40–67	40–81	57–77	37–82	34–82
ECOG PS, n (%)								
0	2	5	1	1	0	2	6	17 (42.5)
1	3	1	5	5	3	5	1	23 (57.5)
Measurable disease at baseline, n (%)	5	5	4	5	1	5	5	30 (75.0)
Visceral disease (liver, lung, peritoneum, pleura, ascites) n (%)	4	3	3	5	0	4	5	24 (60.0)
Number of prior lines of endocrine therapy in any setting, n (%)[a]								
1	0	1	3	1	0	0	0	5 (12.5)
2	2	2	1	2	2	3	2	14 (35.0)
≥3	3	3	2	3	0	4	5	20 (50.0)
Types of prior anticancer therapy in any setting, n (%)								
Chemotherapy	5	1	4	5	2	6	6	29 (72.5)
Aromatase inhibitor	4	6	6	5	2	7	7	37 (92.5)
Fulvestrant	4	5	2	5	0	5	6	27 (67.5)
CDK 4/6 inhibitor	5	6	6	4	2	7	7	37 (92.5)
ESR1 mutations at baseline (ctDNA), n=32 evaluated	3	3	1	3	0	4	2	16 (50.0)[b]

CDK, cyclin-dependent kinase; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]One patient in the 150 mg dose group was missing data as of the data cut-off date. [b]ctDNA was not collected at baseline in 8 patients.

Table 3. Patient Disposition

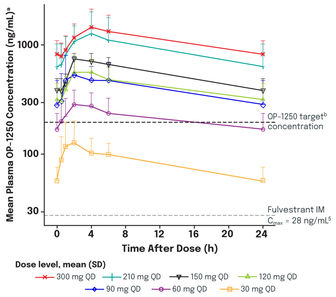
Treatment	30 mg (n=5)	60 mg (n=6)	90 mg (n=6)	120 mg (n=6)	150 mg (n=3)	210 mg (n=7)	300 mg (n=7)	All (N=40)
Treatment ongoing, n	2	2	3	2	3	0	4	16 (40.0%)
Treatment discontinued,[a] n	3	4	3	4	0	7	3	24 (60.0%)

[a]Reasons for treatment discontinuation were: 17 (42.5%) progressive disease, 1 (2.5%) adverse event of febrile neutropenia, and 6 (15%) for other reasons (rising tumor markers [n=2], physician decision [n=1], patient decision [n=1], transfer of care [n=1], HER2+ on post-treatment biopsy [n=1]).

Pharmacokinetics

- OP-1250 is readily bioavailable with a median t_{max} ranging between 2 and 4 hours
- Steady-state OP-1250 plasma concentrations exceed the target efficacious average concentration for dose levels ≥60 mg QD (**Figure 2, Table 4**)
- Dose-proportional increases in OP-1250 exposures (mean C_{max} and AUC_{0-24}) were observed across all evaluated doses after single and multiple doses

Figure 2. OP-1250 Plasma Concentrations Observed Following Repeated Oral Administration on Cycle 2 Day 1



Effective t½=51–73 h, which supports once-daily dosing

[a]24-h OP-1250 imputed using the observed predose value.
[b]Target efficacious C_{avg} value (200 ng/mL) is based on xenograft and cell culture observations. C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; IM, intramuscular; QD, once daily; SD, standard deviation; $t_{1/2}$, half-life.

Table 4. OP-1250 Pharmacokinetics

Dose	C_{max} (ng/mL)	t_{max} (h)[a]	C_{avg} (ng/mL)[b]	AUC_{0-24} (ng*h/mL)[b]	$t_{1/2eff}$ (h)
30 mg n=5	139 (49.6)	2.00 (1.00-6.00)	82.0 (32.7)	1967 (32.7)	54.7 (26.0)
60 mg n=5	292 (38.1)	4.00 (1.00-6.00)	210 (41.1)	5046 (41.1)	63.4 (29.2)[c]
90 mg n=4	540 (42.9)	3.00 (1.00-4.00)	366 (52.4)	8786 (52.4)	72.7 (54.1)
120 mg n=5[d]	614 (30.3)	2.00 (2.00-4.00)	410 (32.1)	9843 (32.1)	68.8 (54.7)
150 mg n=3	789 (11.1)	2.00 (2.00-4.00)	549 (20.3)	13174 (20.3)	61.6 (23.6)
210 mg n=7	1235 (59.9)	4.00 (2.00-4.00)	794 (67.1)	19044 (67.1)	57.3 (109.9)
300 mg n=6	1409 (47.0)	4.00 (2.00-6.00)	1064 (40.3)	25527 (40.2)	51.0 (61.7)

Statistics presented: GeoMean (GeoCV%).
AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; GeoMean, geometric mean; GeoCV%, geometric coefficient of variation; $t_{1/2eff}$, effective half-life; t_{max}, time to maximum concentration.
[a]Median (min–max). [b]24-h OP-1250 imputed using the observed predose value for computation of AUC_{0-24}. [c]n=4. [d]One patient removed as unevaluable for PK

Safety

- Most treatment-emergent adverse events (TEAEs) were grade 1 or 2 at all dose levels (**Table 5**)
- No dose-limiting toxicities (DLTs) were observed and the maximum tolerated dose (MTD) was not reached
- The most common TEAEs were fatigue, nausea, and constipation (**Table 6**)
- Six patients had dose reductions
  - 2 patients at 210 mg dose had reductions: 1 patient to 120 mg and 1 patient to 60 mg
  - 4 patients at 300 mg dose had reductions: 3 patients to 120 mg and 1 patient to 60 mg

Table 5. Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥15% of Patients

	30 mg (n=5)		60 mg (n=6)		90 mg (n=6)		120 mg (n=6)		210 mg (n=7)		300 mg (n=7)		Total (N=37)[a,b]	
Grade	**All**	**G≥3**	**All**	**G≥3**	**All**	**G≥3**	**All**	**G≥3**	**All**	**G≥3**	**All**	**G≥3**	**All (%)**	**G≥3 (%)**
Patients with ≥1 event	5	1	4	0	5	1	6	3	7	2	7	2	34 (91.9)	9 (24.3)
Nausea	2	0	2	0	2	0	5	0	4	0	7	1	22 (59.5)	1 (2.7)
Fatigue	2	0	3	0	0	0	1	0	3	0	4	0	13 (35.1)	0
Constipation	0	0	1	0	1	0	0	0	4	0	3	0	9 (24.3)	0
Headache	1	0	1	0	1	0	1	0	0	0	5	0	9 (24.3)	0
Vomiting	1	0	0	0	1	0	2	1	1	0	4	0	9 (24.3)	1 (2.7)
Decreased appetite	1	0	0	0	1	0	1	0	3	0	2	0	8 (21.6)	0
Neutrophil count decreased	1	1	1	0	0	0	2	1	1	0	2	1	7 (18.9)	3 (8.1)
Rash maculo-papular	1	0	1	0	0	0	1	0	2	0	1	0	6 (16.2)	0

G≥3, grade 3 and 4 events; TEAEs, treatment-emergent adverse events.
[a]150 mg cohort data were not mature as of the data cut-off date and are not included.
[b]Adverse events of interest that did not reach ≥15%
- Two patients at 90 mg and 3 patients at 300 mg experienced photopsia (flashing lights). All events were grade 1 except for 1 event at 300 mg which was grade 2. Ophthalmologic exams were conducted upon symptoms and no detriment in visual acuity or physical abnormalities were reported. There was no interruption in OP-1250 dosing due to photopsia.
- Four patients experienced grade 1 asymptomatic bradycardia; 1 of these 4 was found to have a prior history of asymptomatic bradycardia. One patient was in the 120 mg cohort, 1 patient was in the 210 mg cohort, and 2 patients were in the 300 mg cohort. There was no interruption in OP-1250 dosing due to bradycardia.

Table 6. Adverse Events Attributed to Study Drug by Investigator Occurring in ≥15% of Patients

	30 mg (n=5)		60 mg (n=6)		90 mg (n=6)		120 mg (n=6)		210 mg (n=7)		300 mg (n=7)		Total (N=37)[a,b]	
Grade	**All**	**G≥3**	**All**	**G≥3**	**All**	**G≥3**	**All**	**G≥3**	**All**	**G≥3**	**All**	**G≥3**	**All (%)**	**G≥3 (%)**
Patients with ≥1 event	4	1	3	0	2	0	5	0	6	0	6	1	26 (70.3)	2 (5.4)
Nausea	1	0	2	0	1	0	5	0	4	0	6	1	19 (51.4)	1 (2.7)
Fatigue	2	0	3	0	0	0	1	0	3	0	4	0	13 (35.1)	0
Vomiting	0	0	0	0	1	0	2	0	1	0	4	0	8 (21.6)	0
Headache	0	0	1	0	0	0	1	0	0	0	4	0	6 (16.2)	0

G≥3, grade 3 and 4 events; QD, once daily; TEAEs, treatment-emergent adverse events.
[a]150 mg cohort data were not mature as of the data cut-off date and are not included. [b]Two patients had grade 3/4 neutropenic events attributed to study drug by the investigator that did not reach ≥15%: 1 patient experienced grade 4 neutropenia and grade 4 febrile neutropenia and 1 patient had grade 4 neutropenia. Neutropenia resolved within several weeks of discontinuing study drug.

Efficacy

- Two confirmed partial responses were achieved as of the data cut-off date, each harboring an *ESR1* mutation (1 each in the 60 mg and 120 mg cohorts; **Figure 3**); an additional tumor response occurring in the 30 mg cohort was unconfirmed, as progressive disease occurred at a follow-up visit
- In the clinical benefit rate (CBR)-evaluable population, the CBR was 21% (4/19)
  - CBR is CR + PR + SD ≥24 weeks. The CBR-evaluable population includes patients with measurable and nonmeasurable disease who received at least 1 cycle of treatment, had at least 1 postbaseline tumor assessment, and enrolled ≥24 weeks prior to the data cut-off date
- In the population evaluable for response, the overall response rate (ORR) was 9% (2/23)
  - Includes patients with measurable disease who received at least 1 cycle of treatment and had at least 1 postbaseline tumor assessment

Anticipated RP2D Range

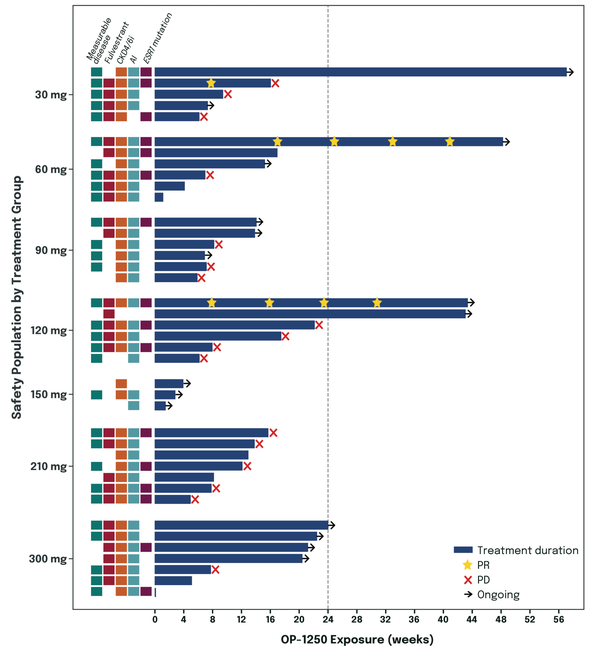
- 60 mg to 120 mg was identified as the anticipated recommended phase 2 dose (RP2D) range
- At 60 mg and above, exposures exceeded the predicted target efficacious average concentration based on preclinical models
- In the cohorts within the anticipated RP2D range, the ORR was 18% and the CBR was 38%
- 2 PRs occurred in the anticipated RP2D range (**Table 7**)

Table 7. Efficacy Response by Cohort in the Anticipated RP2D Range

	Dose cohort			
Efficacy parameter	**60 mg (n=3)**	**90 mg (n=3)**	**120 mg (n=5)**	**Total**
ORR[a] (CR+PR), n	1	0	1	2/11 (18%)
CBR[a,b] (CR+PR+SD ≥24 weeks only), n	1	—	2	3/8 (38%)

CBR, clinical benefit rate; CR, complete response; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SD, stable disease.
[a]ORR and CBR were evaluated per RECIST version 1.1. [b]Includes patients who received at least one cycle of treatment, were evaluable for a response, and enrolled ≥24 weeks prior to the data cut-off date. The data for the 90 mg and 150 mg dose cohorts were not mature for CBR as of the data cut-off date.

Figure 3. Overall Tumor Response (Safety Population)[a]



AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; PD, progressive disease; PR, partial response.
[a]Each lane represents 1 study patient.

Conclusions

- At dose levels of 60 mg and above, OP-1250 demonstrated high and steady exposure levels that were above the predicted efficacious concentration based on preclinical models, supporting once-daily dosing
  - No DLTs were observed and MTD was not reached
  - Most TEAEs were grades 1 or 2 at all dose levels
- Evidence of clinical benefit observed in patients with ER+/HER2– MBC, including those with prior CDK4/6 inhibitor and fulvestrant therapy and those with *ESR1* mutations
- Anticipated dose range of 60 mg to 120 mg identified for RP2D evaluation based on favorable safety and tolerability profile
  - In the anticipated RP2D range, ORR was 18% and CBR was 38%
- Phase 1a dose escalation data continue to mature and updated results will be presented at a future medical meeting
  - As of data cut-off, 16 of 40 patients remain on study
- Further trials of OP-1250 are ongoing and planned
  - Phase 1b dose expansion is ongoing in the targeted dose range at 2 dose levels and will inform selection of RP2D
  - Phase 2 efficacy evaluation is planned to initiate in Q1 2022
  - Combination studies with CDK4/6 and PI3K inhibitors are planned for 2022
- Contact: clinical@olema.com (NCT04505826)

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