

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549**

FORM 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2022

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission file number: 001-39712

OLEMA PHARMACEUTICALS, INC.
(Exact name of Registrant as specified in its charter)

Delaware
(State or other jurisdiction of incorporation or organization)

30-0409740
(I.R.S. Employer Identification No.)

512 2nd Street, 4th Floor
San Francisco, California 94107
(Address of principal executive offices and zip code)
Registrant's telephone number, including area code: (650) 243-5555

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class of Securities Registered	Trading Symbol	Name of Each Exchange on Which Registered
Common Stock, par value \$0.0001 per share	OLMA	The Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES NO

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. YES NO

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES NO

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). YES NO

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	<input type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>	Smaller reporting company	<input checked="" type="checkbox"/>
		Emerging growth company	<input type="checkbox"/>

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report.

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements.

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b).

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). YES NO

The aggregate market value of common stock held by non-affiliates of the Registrant, based on the closing sales price for such stock on June 30, 2022 as reported by The Nasdaq Global Select Market, was \$119,732,713. This calculation excludes 29,418,357 shares held by executive officers, directors and stockholders that the Registrant has concluded are affiliates of the Registrant. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the Registrant.

As of March 3, 2023, the number of outstanding shares of the Registrant's common stock was 40,631,748.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for the 2023 Annual Meeting of Stockholders to be filed with the U.S. Securities and Exchange Commission pursuant to Regulation 14A not later than 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K are incorporated by reference in Part III, Items 10-14 of this Annual Report on Form 10-K.

OLEMA PHARMACEUTICALS, INC.
2022 ANNUAL REPORT ON FORM 10-K
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Unless the context suggests otherwise, references in this Annual Report on Form 10-K, or the Annual Report, to “us,” “our,” “Olema,” “Olema Pharmaceuticals,” “we,” the “Company” and similar designations refer to Olema Pharmaceuticals, Inc. and, where appropriate, its subsidiary.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report contains forward-looking statements that involve risks, uncertainties and assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. The statements contained in this Annual Report that are not purely historical are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Forward-looking statements are often identified by the use of words such as, but not limited to, “anticipate,” “believe,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would” or the negative of those terms, and similar expressions that convey uncertainty of future events or outcomes to identify these forward-looking statements. Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements. Forward-looking statements in this Annual Report include, but are not limited to, statements about:

- our financial performance;
- the sufficiency of our existing cash to fund our future operating expenses and capital expenditure requirements;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements, and needs for additional financing;
- the scope, progress, results and costs of developing OP-1250 or any other product candidates we may develop, and conducting nonclinical studies and clinical trials, including our OP-1250 Phase 1/2 clinical study;
- the timing and costs involved in obtaining and maintaining regulatory approval of OP-1250 or any other product candidates we may develop, and the timing or likelihood of regulatory filings and approvals, including our expectation to seek special designations for our product candidates for various diseases;
- our plans relating to commercializing OP-1250 and any other product candidates we may develop, if approved, including the geographic areas of focus and our ability to grow a sales team;
- the implementation of our strategic plans for our business and OP-1250 or any other product candidates we may develop;
- the size of the market opportunity for OP-1250 or any other product candidates we may develop in each of the diseases we target;
- our reliance on third parties to conduct nonclinical research activities, and for the manufacture of OP-1250 and any other product candidates we may develop;
- the beneficial characteristics, safety, efficacy and therapeutic effects of OP-1250 and any other product candidates we may develop;
- our estimates of the number of patients in the United States who suffer from the diseases we target and the number of subjects that will enroll in our clinical trials;
- the progress and focus of our current and future clinical trials, and the reporting of data from those trials;
- our ability to advance product candidates into and successfully complete clinical trials;

- the ability of our clinical trials to demonstrate the safety and efficacy of OP-1250 and any other product candidates we may develop, and other positive results;
- the success of competing therapies that are or may become available;
- developments relating to our competitors and our industry, including competing product candidates and therapies;
- our plans relating to the further development and manufacturing of OP-1250 and any other product candidates we may develop, including additional indications that we may pursue;
- existing regulations and regulatory developments in the United States and other jurisdictions;
- our potential and ability to successfully manufacture and supply OP-1250 and any other product candidates we may develop for clinical trials and for commercial use, if approved;
- the rate and degree of market acceptance of OP-1250 and any other product candidates we may develop, as well as the pricing and reimbursement of OP-1250 and any other product candidates we may develop, if approved;
- our continued reliance on third parties to conduct additional clinical trials of OP-1250 and any other product candidates we may develop, and for the manufacture of our product candidates;
- our plans and ability to obtain and protect intellectual property rights;
- the scope of protection we are able to establish and maintain for intellectual property rights, including OP-1250 and any other product candidates we may develop;
- our ability to access capital resources on favorable terms, or at all;
- our ability to retain the continued service of our key personnel and to identify, hire, and then retain additional qualified personnel; and
- our expectations regarding the impact of the COVID-19 pandemic on our business and operations, including clinical trials, manufacturing suppliers, collaborators, use of contract research organizations, or CROs, and employees.

These statements are based on the beliefs and assumptions of our management, which are in turn based on information currently available to management. Such forward-looking statements are subject to risks, uncertainties and other important factors that could cause actual results and the timing of certain events to differ materially from future results expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section entitled “Risk Factors” included under Part I, Item 1A below. Furthermore, such forward-looking statements speak only as of the date of this Annual Report. Except as required by law, we undertake no obligation to update any forward-looking statements to reflect events or circumstances after the date of such statements.

RISK FACTOR SUMMARY

Investing in our common stock involves numerous risks, including the risks described in “Part I, Item 1A. Risk Factors” of this Annual Report. Below are some of these risks, any one of which could materially adversely affect our business, financial condition, results of operations, and prospects.

- We have not completed any clinical trials and have no products approved for commercial sale, which may make it difficult for you to evaluate our current business and predict our future success and viability.
- We require substantial additional capital to finance our operations. If we are unable to raise such capital when needed, or on acceptable terms, we may be forced to delay, reduce and/or eliminate one or more of our research and drug development programs of our only product or future commercialization efforts.
- We have incurred net losses since inception, and we expect to continue to incur net losses for the foreseeable future. We expect to continue to incur increased expenses and operating losses for the foreseeable future as we continue our research and development efforts and seek to obtain regulatory approval for OP-1250. In addition, we may be unable to continue as a going concern over the long term.
- We are substantially dependent on the success of our only product candidate, OP-1250, which is currently in the early stages of clinical development. We cannot assure you that our planned clinical development programs for OP-1250 will be completed in a timely manner, or at all, or that we will be able to obtain approval for OP-1250 from the FDA, or any comparable foreign regulatory authority. If we are unable to complete development of, obtain regulatory approval for and commercialize OP-1250 in one or more indications and in a timely manner, our business, financial condition, results of operations and prospects will be significantly harmed.
- Clinical development is a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results. Failure can occur at any stage of clinical development. We have never completed a pivotal clinical trial or submitted a New Drug Application, or NDA, to the FDA or similar drug approval filings to comparable foreign authorities. If we are ultimately unable to obtain regulatory approval for OP-1250, we will be unable to generate product revenue and our business, financial condition, results of operations and prospects will be significantly harmed.
- Even if approved, OP-1250 may not achieve adequate market acceptance among physicians, patients, healthcare payors and others in the medical community necessary for commercial success. The degree of market acceptance would depend on a number of factors. If OP-1250 is approved but does not achieve an adequate level of acceptance by physicians, hospitals, healthcare payors and patients, we may not generate or derive sufficient revenue and could significantly harm our business, financial condition, results of operations and prospects.
- We face significant competition, and if our competitors develop and market technologies or products more rapidly than we do or that are more effective, safer or less expensive than OP-1250, or product candidates we may develop in the future, our commercial opportunities will be negatively impacted.
- We may be unable to obtain U.S. or foreign regulatory approvals and, as a result, may be unable to commercialize OP-1250 or any future product candidate we may develop.
- The COVID-19 pandemic could adversely impact our business, including our nonclinical studies and clinical trials.
- Unfavorable U.S. and global macroeconomic and geopolitical conditions could adversely affect our business, financial condition and results of operations.
- In order to successfully implement our plans and strategies, we will need to grow the size of our organization, and we may experience difficulties in managing this growth. Given the small size of our organization, we may encounter difficulties managing multiple clinical trials at the same time, which could negatively affect our ability to manage the growth of our organization, particularly as we take on additional responsibility associated with being a public company. If we are not able to effectively expand our organization by hiring new employees and/or engaging additional third-party service providers, we may not be able to successfully implement the tasks necessary to further develop and commercialize

OP-1250 and any other future product candidates we may develop and, accordingly, may not achieve our research, development and commercialization goals.

- Our internal computer systems, or those of any of our CROs, manufacturers, other contractors, consultants, collaborators or potential future collaborators, or other third parties (including service providers in our supply chain) may fail or suffer security or data privacy breaches or other unauthorized or improper access to, use of, or destruction of our proprietary or confidential data, employee data, or personal data, which could result in additional costs, loss of revenue, significant liabilities, harm to our brand and material disruption of our operations.
- Our success depends on our ability to protect our intellectual property and our proprietary technologies. Even issued patents may later be found invalid or unenforceable or may be modified or revoked in proceedings instituted by third parties before various patent offices or in courts. Thus, the degree of future protection for our proprietary rights is uncertain.
- We rely, and expect to continue to rely, on third parties, including independent clinical investigators and CROs to conduct certain aspects of our nonclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties, comply with applicable regulatory requirements or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize OP-1250 or future product candidates we may develop and our business, financial condition, results of operations and prospects could be significantly harmed.
- We qualify as a “smaller reporting company” within the meaning of the Exchange Act and may take advantage of certain exemptions from disclosure requirements available to smaller reporting companies, which could make our securities less attractive to investors and may make it more difficult to compare our performance to the performance of other public companies.

Part I

Item 1. Business.

Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of next generation targeted therapies for women's cancers. Our team has spent the past decade characterizing the structure and function of the estrogen receptor, or ER, a key driver of breast cancer in approximately 75% of patients, in order to develop more potent, oral therapies that completely inactivate this signaling pathway. Our lead product candidate, OP-1250, is a novel oral therapy with combined activity as both a complete ER antagonist, or CERAN, and a selective ER degrader, or SERD, which we believe will drive deeper, more durable responses than existing therapies. OP-1250, both as a monotherapy and in combination with inhibitors of cyclin-dependent kinase 4 and 6, or CDK4/6, demonstrated robust anti-tumor activity in a range of preclinical xenograft models of breast cancer, including in ESR1 and PIK3CA mutations and central nervous system, or CNS, metastasis. In August 2020, we initiated an ongoing Phase 1/2 monotherapy dose escalation and expansion study evaluating OP-1250 for the treatment of recurrent, locally advanced or metastatic ER-positive, or ER+, human epidermal growth factor receptor 2-negative, or HER2-, breast cancer. We reported initial data from the Phase 1a dose escalation portion of this study in November 2021, which provided proof-of-concept for OP-1250 as a monotherapy treatment for ER+/HER2- breast cancer. We reported additional monotherapy data from the Phase 1b dose expansion portion of this study in October 2022 and initiated the Phase 2 portion of the study. In 2022, we also initiated Phase 1b/2 dose escalation and expansion studies evaluating OP-1250 in combination with CDK4/6 inhibitors palbociclib and ribociclib and phosphatidylinositol 3 kinase alpha, or PI3K α inhibitor, alpelisib. In December 2022, we reported initial data from the Phase 1a dose escalation portion of the study in combination with palbociclib which demonstrated attractive combinability including no drug-drug interaction, or DDI, between the two agents. In July 2022, we were granted Fast Track designation from the U.S. Food and Drug Administration, or FDA, for OP-1250 for patients with ER+/HER2- metastatic breast cancer that has progressed following one or more lines of endocrine therapy with at least one line given in combination with a CDK4/6 inhibitor. Based on the clinical results we have achieved to date, we are advancing OP-1250 through to late-stage clinical development both as a monotherapy and in combination with other targeted agents. We own worldwide development and commercialization rights to OP-1250. We believe OP-1250's oral formulation and dual mechanism of action directly address the limitations of current endocrine therapies, such as fulvestrant and tamoxifen, and position OP-1250 as a potential endocrine therapy of choice for the treatment of ER+ breast cancers. Our goal is to transform the standard of care for women living with cancers by developing more effective therapies that apply our deep understanding and collective expertise in endocrine-driven cancers, nuclear receptor activities and mechanisms of acquired resistance.

We are initially focused on developing therapies for the treatment of breast cancer, which represents approximately 30% of all new diagnoses of cancer in women. In 2022, the American Cancer Society, or ACS, estimated there were approximately 288,000 new cases of female breast cancer and over 43,250 deaths from metastatic breast cancer in the United States. Treatment decisions are based on a combination of individual patient characteristics and tumor biology, most importantly the expression of three proteins: ER, progesterone receptor, or PR, and human epidermal growth factor receptor 2, or HER2. Approximately 75% of all breast cancers are ER+, and approximately 68% are HR+/HER2-, highlighting the central role of the ER in driving a large majority of breast cancer. Approximately 6-10% of breast cancer patients present with metastatic disease at diagnosis and a further 20-30% of patients initially diagnosed with early-stage disease ultimately develop metastatic disease. The current five-year survival rate for patients with ER+ metastatic breast cancer is approximately 30%. In 2020, the breast cancer therapy market totaled \$22.3 billion, and it is set to grow at a CAGR of 8.7%, reaching \$51.3 billion in 2030. All key breast cancer populations will experience strong sales growth. We expect sales in the HR+/HER2- population to rise from \$11.3 billion in 2020 to \$30.6 billion in 2030.

The ER is a nuclear receptor that functions as a ligand regulated transcription factor. When bound to estrogen, the ER directs the expression of genes that are essential for breast cancer cells' survival and proliferation. For more than four decades, researchers have been developing new approaches and therapies to prevent activation of the ER pathway, thereby inhibiting the ability of the ER to drive tumor cell growth. In 1977, the first endocrine therapeutic, the anti-estrogen tamoxifen, was approved by the FDA for the treatment of breast cancer. Tamoxifen is still commonly used today but is challenged by the development of acquired drug resistance, which in some cases may be due to its partial agonist activity. In search for a different mechanism to target the estrogen pathway, aromatase inhibitors, or AIs, were developed in the 1990s to block the synthesis of estrogen and deprive the ER+ cells of its activating ligand. However, up to 50% of patients taking AIs develop arthralgia, leading to suspension of treatment in up to 15% of patients. Additionally, most patients with metastatic breast cancer have been shown to ultimately develop resistance to AIs, the most common of which is the development of a ligand-independent activating mutation in the estrogen receptor gene, ESR1. AIs are also not used to treat pre-menopausal women without the addition of ovarian suppression.

In 2002, fulvestrant was approved as a treatment for hormone receptor positive, or HR+, metastatic breast cancer patients and is typically used as a second- or third-line endocrine agent. Fulvestrant was designed to be a CERAN, and later discovered to also be a SERD, and represented a breakthrough for the field with improved outcomes for patients whose disease had progressed on prior endocrine therapy. However, fulvestrant has several limitations including its suboptimal drug exposure and route of administration as a monthly intramuscular injection. Despite these drawbacks, fulvestrant achieved worldwide sales of over \$1.1 billion in 2019.

More recently, the field has focused on the discovery and development of oral agents that have fulvestrant's dual mechanism of action to completely inactivate and degrade the ER. Some of these oral SERD agents are CERANs, such as OP-1250, but others have partial agonist activity despite being SERDs and thus are not CERANs. These agents can be considered selective ER modulators, or SERM/SERDs. SERM/SERDs reduce the levels of the ER but they do not entirely eliminate it. Notably, naturally-occurring estrogen itself leads to ER degradation when binding the ER.

We designed our lead product candidate, OP-1250, based both on a detailed structural understanding of the ER and on known alterations to this structure induced by fulvestrant and other ligands. We have demonstrated in nonclinical studies that OP-1250 functions both as a CERAN and a SERD, but is distinguished from fulvestrant in several noteworthy ways, including:

- OP-1250 is orally bioavailable while fulvestrant is a highly insoluble compound that must be administered monthly by intramuscular injection into the buttocks;
- OP-1250 has favorable biodistribution properties leading to significantly higher drug concentrations in the plasma and tumor than those achieved with fulvestrant; and
- OP-1250 has demonstrated the ability to shrink tumors in head-to-head nonclinical studies with fulvestrant, in contrast to fulvestrant, which has only been shown to inhibit tumor growth.

Based on these differences, we believe that OP-1250 has the potential to demonstrate clinical outcomes superior to fulvestrant. Furthermore, OP-1250 has the potential to benefit patients with metastatic breast cancer, initially for patients who have previously received endocrine therapy, as well as those who are treatment naïve in the metastatic setting, and advance into the adjuvant setting for early-stage ER+ breast cancer. In multiple nonclinical animal models of anti-cancer activity, including patient-derived xenografts with tumors containing activating mutations in the ER, OP-1250 monotherapy led to tumor shrinkage or in some cases tumor eradication, as well as long-term post-treatment survival. In each of these nonclinical models, the effect of OP-1250 was superior to that of fulvestrant, an effect which we determined was driven both by improved pharmacokinetics, or PK, properties, and higher plasma and tumor drug concentrations. In nonclinical studies, OP-1250 demonstrated robust CNS penetration, and in an intracranial breast cancer brain metastases xenograft study, OP-1250 demonstrated the ability to shrink tumors and improve survival in mice. OP-1250 has

the potential to address a critical unmet medical need as 10-15% of ER+ breast cancer patients develop brain metastases for which there are currently limited treatment options. In addition, we believe that combining OP-1250 with HER2 targeted agents may represent an opportunity to improve upon recent advancements in the treatment of CNS disease in patients that express both ER and HER2, as up to 50% of patients with metastatic HER2+ breast cancer develop CNS disease, and the majority of patients with HER2+ breast cancer also express ER. In nonclinical studies, the addition of OP-1250 to HER2 inhibitors improved tumor growth inhibition in both ER+/HER2+ cell line-derived xenograft and patient-derived xenograft models.

As summarized in our pipeline figure below, our plan is to develop our wholly-owned lead product candidate, OP-1250, in a number of ER+ breast cancer indications, both as a monotherapy and in combination with approved targeted therapies that have shown improved outcomes with other endocrine therapies.

Figure 1. Olema product pipeline



In August 2020, we initiated a Phase 1/2 clinical study of OP-1250 in patients with recurrent, locally advanced or metastatic ER+/HER2- breast cancer whose disease has progressed on endocrine therapy. Phase 1a consisted of monotherapy dose escalation to evaluate the safety and PK of OP-1250 and to determine the maximum tolerated dose, or MTD, and/or the recommended Phase 2 dose, or RP2D. In November 2021, we reported interim Phase 1a data, with OP-1250 demonstrating attractive PK with oral bioavailability and dose-proportional exposures supporting once daily dosing; favorable tolerability with no maximum tolerated dose defined, and no clinically significant bradycardia, ocular toxicity or diarrhea; and evidence of single-agent activity in patients who had advanced on multiple prior therapies in the advanced setting, including CDK4/6 inhibitors, and confirmed partial responses in patients with baseline estrogen receptor 1, or ESR1, activating mutations.

In 2022, we completed enrollment in our Phase 1b dose expansion at two dose levels (60 mg and 120 mg daily) and selected 120 mg daily as our RP2D to advance into Phase 2 efficacy evaluation. Phase 2 efficacy

evaluation initiated in the second half of 2022 with approximately 80 patients expected to be enrolled across three cohorts: patients with measurable disease (n=50), patients with non-measurable disease (n=15), and patients with CNS metastasis (n=15). The first two primary cohorts, patients with measurable disease and patients with non-measurable disease, were fully enrolled in the fourth quarter of 2022.

In October 2022, we reported preliminary Phase 1b clinical data at the 34th EORTC-NCI-AACR Symposium, with OP-1250 demonstrating attractive PK with oral bioavailability and high drug exposure, supporting once daily dosing; favorable tolerability with no dose-limiting toxicities and no maximum tolerated dose defined; and strong anti-tumor activity and durable benefit with 41% of patients seeing reductions in target tumor lesions, a 39% clinical benefit rate, or CBR, at our RP2D of 120 mg (seven out of 18 CBR-eligible patients) and six partial responses (four confirmed and two unconfirmed) out of 57 efficacy-evaluable patients. We believe that with this profile, OP-1250 has the potential to become the endocrine therapy of choice for the treatment of ER+/HER2- breast cancer. We anticipate presenting Phase 2 clinical data for OP-1250 as a monotherapy in the second half of 2023.

Based on our clinical results to date, we intend to discuss plans to initiate a pivotal Phase 3 monotherapy trial in second- and third-line advanced or metastatic breast cancer patients at an End of Phase 2 meeting with the FDA and the European Medicines Agency, or EMA, prior to initiating such trial in what we expect to be the second half of 2023.

In January 2022, we initiated a Phase 1b dose escalation study evaluating OP-1250 in combination with the CDK4/6 inhibitor palbociclib for the treatment of recurrent, locally advanced or metastatic ER+/HER2 breast cancer. We presented preliminary results from this Phase 1b study in December 2022 at the 2022 San Antonio Breast Cancer Symposium. Across 12 patients, the combination of up to 120 mg of OP-1250 with 125 mg of palbociclib was shown to be well tolerated with no DDI, no induced metabolism of palbociclib, and exposure of OP-1250 in combination with palbociclib was consistent with the observed monotherapy OP-1250 exposure levels. In addition, there was no dose-related increase in the incidence or severity of adverse events, and neutropenia events observed were consistent with the expected profile of palbociclib plus an endocrine therapy. In the third quarter of 2022, we initiated the Phase 2 dose expansion portion of this study with 120 mg of OP-1250 in combination with 125 mg of palbociclib. We anticipate presenting results from this Phase 2 study in the second quarter of 2023.

Concurrently, in the third quarter of 2022, we initiated a Phase 1b dose escalation study of OP-1250 in combination with CDK4/6 inhibitor, ribociclib, and PI3K α inhibitor, alpelisib, which have both been shown to lead to improvements in both progression-free and overall survival. These studies are ongoing and we anticipate presenting data from the Phase 1b clinical study for OP-1250 in combination with ribociclib in the second half of 2023. In July 2022, we were granted Fast Track designation from the FDA for OP-1250 for the treatment of ER+/HER2- metastatic breast cancer that has progressed following one or more lines of endocrine therapy with at least one line given in combination with a CDK4/6 inhibitor.

In July 2020, we entered into a non-exclusive agreement with Novartis Institutes for BioMedical Research, Inc., or Novartis, to evaluate the combination of OP-1250 and Novartis' KISQALI® (ribociclib), a CDK4/6 inhibitor, as well as PIQRAY® (alpelisib), their PI3K α inhibitor. Under the terms of the collaboration, Novartis will be responsible for funding a capped majority of the costs for the Phase 1b clinical study, as well as supplying their drugs. In November 2020, we entered into a non-exclusive agreement with Pfizer Inc., or Pfizer, to evaluate the safety and tolerability of OP-1250 in combination with Pfizer's CDK4/6 inhibitor IBRANCE® (palbociclib) in patients with recurrent, locally advanced or metastatic ER+/HER2- breast cancer. Under the terms of the non-exclusive agreement, we will be responsible for conducting the clinical study for the combined therapy and Pfizer is responsible for supplying IBRANCE® (palbociclib) at no cost to us. As part of the collaboration, the parties granted to each other a non-exclusive, royalty-free license under certain of the parties' respective patent rights in the combination of IBRANCE® and OP-1250 to use the parties' respective study drugs in research and development, solely to the extent reasonably needed for the other party's activities in the collaboration. All inventions and data developed in the performance of the clinical trials for the combined therapies (other than those specific to each component study drug), will be jointly owned by the parties.

We expect to present additional monotherapy and combination therapy data in 2023 and initiate a pivotal Phase 3 monotherapy trial of OP-1250 in the second- and third-line settings of ER+/HER2- advanced or metastatic breast cancer in the second half of 2023, subject to feedback from the FDA and EMA.

Our Strategy

Our goal is to discover, develop and commercialize next generation targeted therapies for women's cancers. The key elements of our business strategy to achieve this goal include:

- **Applying our deep understanding of nuclear receptors — particularly the ER — and mechanisms of resistance to develop novel therapeutic approaches for endocrine-driven cancers.** Our team has spent over a decade characterizing the structure and function of the ER and its role in driving tumor cell proliferation in HR+ breast cancer. Our knowledge of the ER's functional domains combined with our medicinal chemistry expertise has allowed us to develop a potent and oral compound that both completely inactivates and strongly promotes degradation of the ER in nonclinical studies. We believe OP-1250's oral formulation and dual mechanism of action as a CERAN/SERD directly address the limitations of current endocrine therapies, such as fulvestrant and tamoxifen, and has the potential to drive deeper, more durable responses.
- **Rapidly advancing our lead product candidate, OP-1250, through clinical development as a monotherapy for ER+/HER2 breast cancer.** We are currently evaluating OP-1250 monotherapy in a Phase 1/2 dose escalation and expansion clinical study in patients with recurrent, locally advanced or metastatic ER+/HER2 breast cancer whose disease has progressed on endocrine therapy. We plan to initiate a pivotal Phase 3 trial for OP-1250 as a monotherapy agent in the second- and third-line setting of ER+/HER2- advanced or metastatic breast cancer in the second half of 2023, subject to feedback from the FDA and EMA.
- **Establishing OP-1250 as the endocrine therapy of choice with targeted therapy combinations for the treatment of metastatic ER+ breast cancers.** We believe OP-1250's differentiated product profile has the potential to overcome many of the limitations of current endocrine therapy options. While targeted chemotherapy and other targeted anti-body drug conjugates continue to show promising data and will likely gain further favorability as a treatment option, we believe these new treatment options will replace traditional chemotherapy, not endocrine therapies. Our goal is to successfully demonstrate improved efficacy and a favorable tolerability profile in combination with other targeted therapies in order to position OP-1250 as the endocrine therapy of choice in the first-line setting for advanced or metastatic ER+/HER2- breast cancer.
- **Exploring additional clinical opportunities for OP-1250, including metastatic breast cancer with brain metastases and other hormone sensitive tumors.** Metastatic breast cancer is the second most common cancer associated with brain metastases in the United States. Of women with ER+/HER2- metastatic breast cancer, 10% to 15% will develop brain metastases, which present a significant challenge to systemic therapy. The primary treatment for CNS metastases is typically surgery, radiation, or a combination of both and these patients tend to have a poor prognosis. In nonclinical studies, OP-1250 demonstrated robust CNS penetration, and in an intracranial breast cancer brain metastases xenograft study, OP-1250 demonstrated the ability to shrink tumors and improve survival in mice. In addition, we believe that combining OP-1250 with HER2 targeted agents may represent an opportunity to improve upon recent advancements in the treatment of CNS disease in patients that express both ER and HER2, as up to 50% of patients with metastatic HER2+ breast cancer develop CNS disease, and the majority of patients with HER2+ breast cancer also express ER. In nonclinical studies, the addition of OP-1250 to HER2 inhibitors improved tumor growth inhibition in both ER+/HER2+ cell line-derived xenograft and patient-derived xenograft models.
- **Continuing to evaluate opportunities to accelerate development timelines and enhance the commercial potential of our programs in collaboration with third parties.** We own full worldwide

development and commercialization rights to OP-1250. We have established clinical collaborations with both Novartis and Pfizer and we intend to continue evaluating opportunities to work with partners that meaningfully enhance our capabilities with respect to the development and commercialization of OP-1250. In addition, we intend to commercialize our product candidates in key markets either alone or with partners in order to maximize the worldwide commercial potential of our programs.

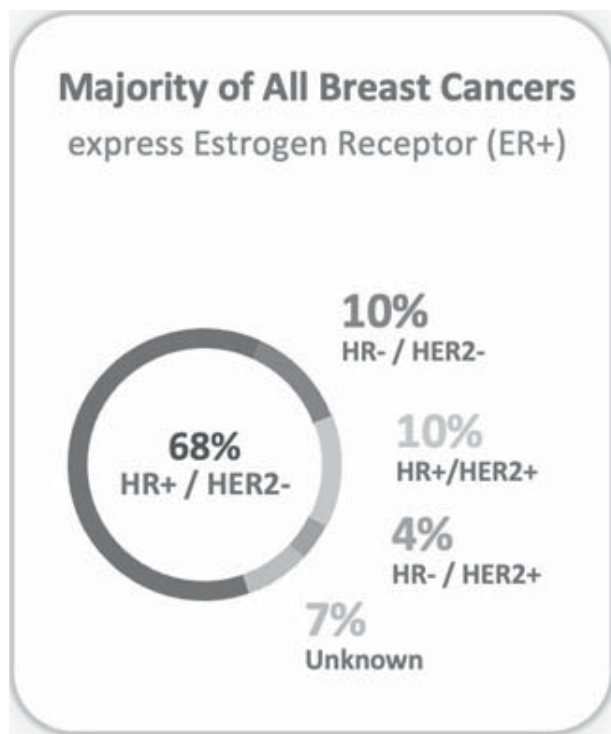
- **Expanding our portfolio of therapies focused on women’s oncology through both internal research activities and business development efforts.** We are applying our internal drug discovery capabilities to identify and evaluate novel targeted therapies that can improve the lives of women with cancer. We have an active discovery research team exploring additional opportunities for targeted therapies for breast cancer. We will also continue to explore opportunities to acquire products and technologies that align with our core areas of expertise and complement our existing portfolio.

Our Opportunity

Epidemiology and classification of breast cancer

Breast cancer is the second-most common cancer worldwide, with nearly two million new diagnoses per year. In 2022, the ACS estimated there were approximately 288,000 new cases of female breast cancer and over 43,250 deaths in the United States, making it the second-leading cause of cancer death in women. Approximately 2,700 men are also diagnosed with breast cancer each year in the United States. Breast cancer is a heterogeneous disease which is grouped into several clinical subtypes based on the expression of three proteins: ER, PR and HER2. Both ER and PR are hormone receptors, and tumors that express either of these receptors are referred to as HR+. It is unusual for a tumor to express PR in the absence of the ER, therefore most tumors are referred to as either ER+ or ER-. Tumors that express HER2 are denoted HER2+, and tumors that do not express ER, PR or HER2 are classified as triple negative breast cancer. Approximately 78% of all breast cancers are HR+, and approximately 68% are HR+/HER2-, highlighting the central role of ER signaling in driving a large majority of breast cancer. The percentage breakdown of all breast cancers by subtype are shown in Figure 2.

Figure 2. Types of breast cancer



Treating breast cancer

Early-stage breast cancer

Breast cancer stage is determined by the size of the tumor and whether or not the cancer has spread to lymph nodes. A tumor that is confined to the breast with or without the involvement of local, ipsilateral lymph nodes is considered early-stage breast cancer. Treatment for patients with early-stage breast cancer involves two components. First, there is local treatment of the breast, chest wall and local lymph nodes, if any, with surgery, either a lumpectomy or mastectomy, and potentially radiation. Second, based on the biology and characteristics of the tumor, patients may also be offered systemic therapy, referred to as adjuvant therapy, in order to decrease the risk of recurrence of breast cancer anywhere in the body. Systemic therapy can be given either after surgery (adjuvant) or prior to surgery (neoadjuvant) or a combination of both.

The initial standard of care for patients with early-stage ER+ breast cancer is at least five years of adjuvant endocrine therapy. The endocrine treatment options for early-stage disease are AIs, such as anastrozole, exemestane or letrozole, or an ER antagonist such as a tamoxifen. For patients diagnosed with early-stage ER+ breast cancer who undergo surgical and adjuvant/neoadjuvant treatment, the five-year survival rate is over 90%.

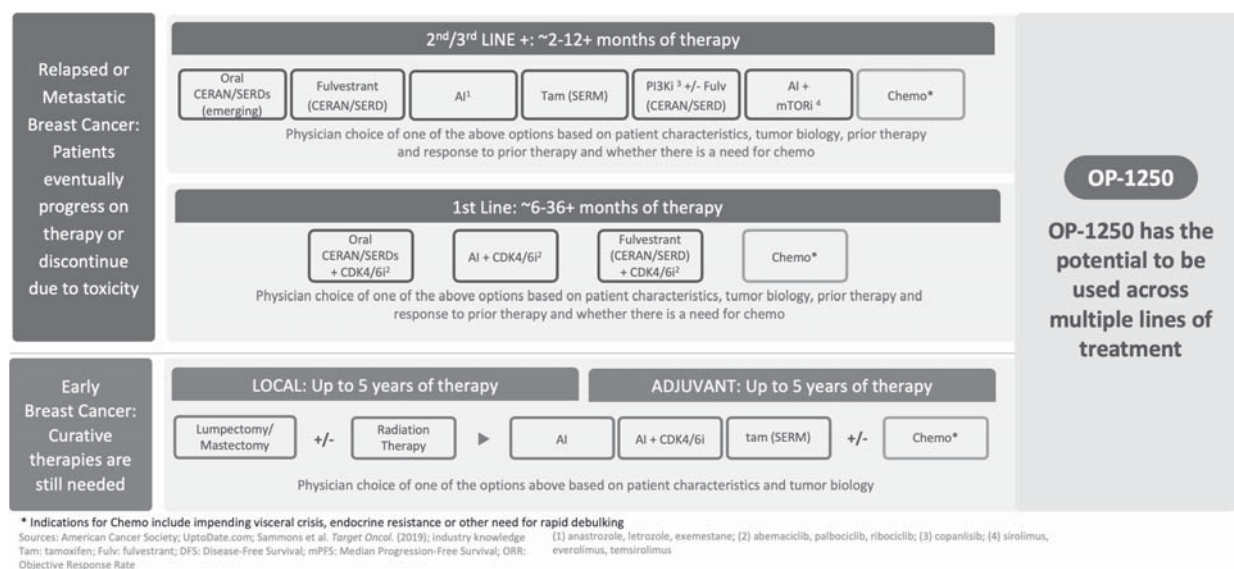
Metastatic breast cancer

When cancer has spread beyond local lymph nodes, either to distant lymph nodes, bones or visceral organs, the cancer is now considered metastatic. Approximately 6-10% of breast cancer patients present with de novo metastatic disease, also referred to as stage IV disease, at initial diagnosis. In addition, approximately 20-30% of patients diagnosed with early-stage breast cancer will develop metastatic disease. In contrast to the goals of

adjuvant therapy, treatments for metastatic disease are palliative with the desired outcome of controlling symptoms and extending survival as long as possible. The current five-year survival rate for patients with ER+ metastatic breast cancer is approximately 30%.

While there are national guidelines and recommendations for the treatment of metastatic breast cancer, the actual treatment decision is based on a combination of individual patient characteristics and tumor biology, including whether they received adjuvant therapy and if so, how quickly the cancer recurred. There is significant overlap in the agents that are recommended, but guidelines vary in the sequence in which these agents are used. In the past five years, several new classes of targeted therapies have been approved to be used in combination with endocrine agents for the treatment of HR+/HER2- breast cancer. Inhibitors of CDK4/6, such as palbociclib, ribociclib and abemaciclib, used in combination with an AI or fulvestrant, led to significant increases in progression-free survival and overall survival. Alpelisib, a PI3K α inhibitor, was approved in 2019 in combination with fulvestrant for the treatment of HR+/HER2- breast cancers that have mutations in PIK3CA. Figure 3 shows the endocrine treatment options available for ER+ metastatic breast cancer, and an example of the sequence of treatments, by agent and line of therapy.

Figure 3. Available endocrine options and example of sequential alternating of endocrine based therapy in ER+ metastatic breast cancer



When moving a patient from one line of therapy to the next, the standard of care is to switch to an endocrine agent with a different mechanism of action depending upon last therapy, co-morbidities, and individual patient characteristics.

Metastatic breast cancer is the second most common cancer associated with brain metastases in the United States. About 10% to 15% of women with metastatic breast cancer develop brain metastases. Brain metastases present a significant challenge to systemic therapy, and the primary treatment for CNS metastases is typically surgical resection, radiation, or a combination of both. Given the limited treatment options available for these patients, the prognosis remains poor, making it an area of continued, high unmet medical need. In addition, brain metastases in breast cancer patients are a major cause of morbidity, associated with progressive neurologic deficits that result in a reduced quality of life.

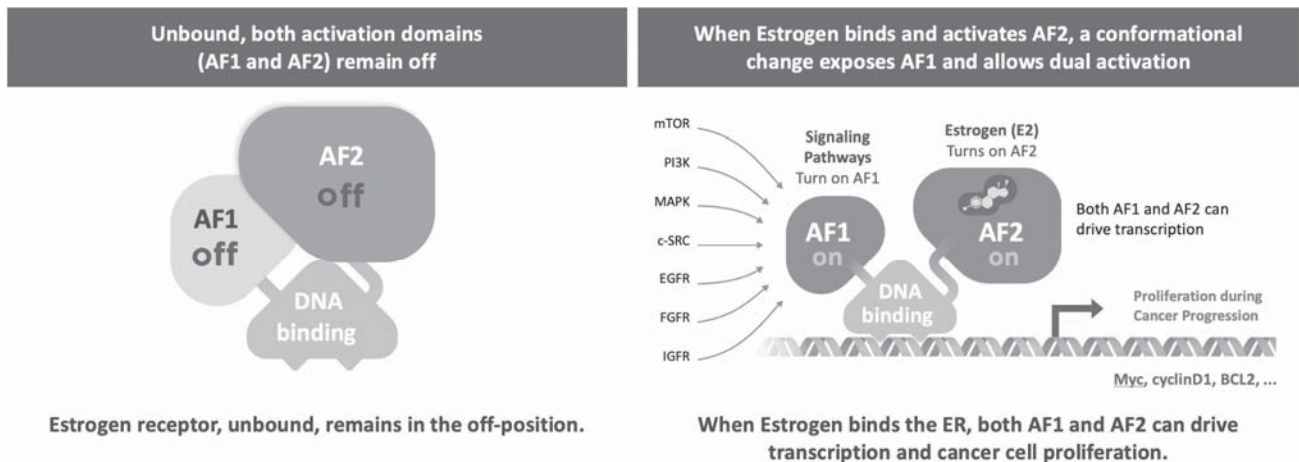
ER signaling in cancer

The ER is a nuclear receptor that functions as a ligand regulated transcription factor. When bound to estrogen, the ER directs the expression of genes that are essential for breast cancer cells' survival and proliferation. The ER has three modular functional domains:

- The amino terminal domain, which contains the activation function 1, or AF1, the activity of which can be increased by multiple cell proliferative signaling pathways;
- The DNA binding domain, which directs the ER to bind to a specific set of ER-responsive genes; and
- The ligand binding domain, which contains the activation function 2, or AF2, which is turned on when bound to estrogen.

Activation of either AF1 or AF2 can drive transcription and cancer cell proliferation.

Figure 4. ER is a tripartite protein with two distinct transcription factor activation domains, AF1 and AF2

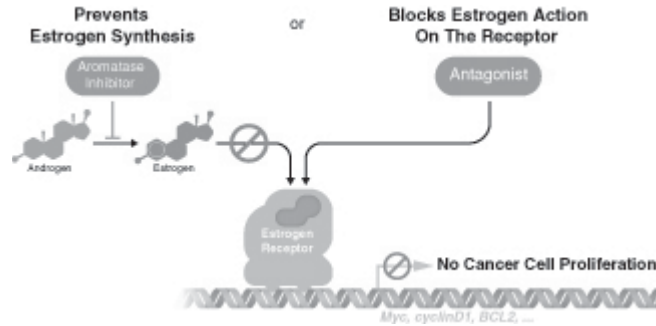


References: Shang and Brown, Science, 29 Mar 2002; Vol. 295, Issue 5564, pp. 2465-2468. Webb, Nguyen, and Kushner, JBC, Vol. 278, 28 Feb 2003, pp. 6912-6920

Classes of endocrine therapies and their limitations

For more than four decades, researchers have been developing new approaches and therapies to prevent activation of the ER pathway, thereby inhibiting the ability of the ER to drive tumor cell growth. Figure 5 describes the two major classes of endocrine therapies, AIs and ER antagonists. In 2020, worldwide sales for endocrine and targeted therapies treating ER+ breast cancer patients totaled \$20.5 billion.

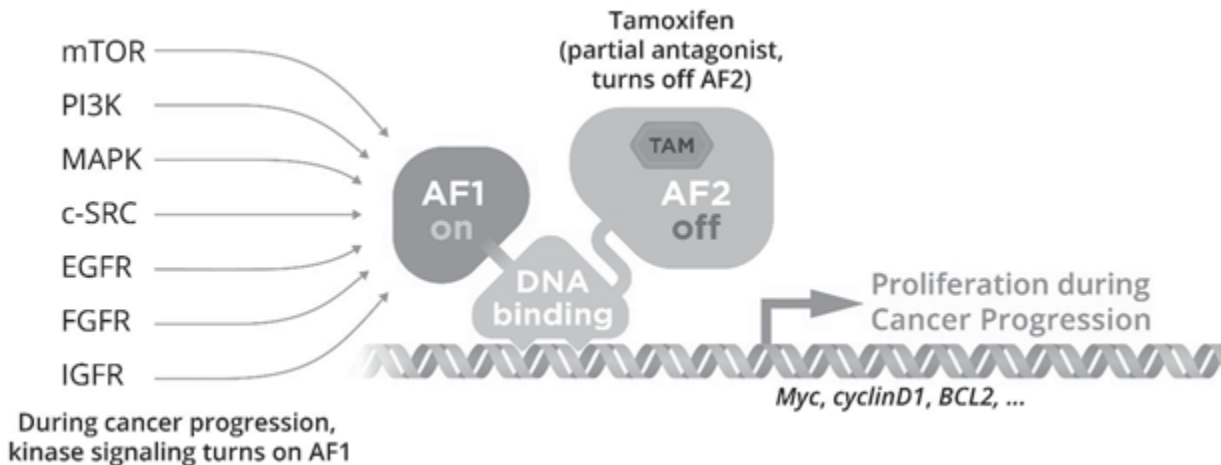
Figure 5. Classes of endocrine therapies



Antagonists with partial agonist activity

In 1977, the first endocrine therapeutic, tamoxifen, was approved by the FDA for the treatment of breast cancer. Although tamoxifen directly competes with estrogen and prevents activation of the AF2 transcription factor activation domain, it does not block AF1 activity and therefore does not completely inhibit ER function (Figure 6). As a consequence of this partial agonist activity, tamoxifen mimics estrogen in some circumstances and promotes proliferation. In addition, some breast cancers can develop resistance to these partial agonists by activation of upstream AF1 signaling pathways, such as mTOR, PI3K, MAPK, c-SRC, EGFR, FGFR and IGFR. Therefore, while tamoxifen is commonly used today, it is challenged by acquired drug resistance and a relatively short duration of response.

Figure 6. Partial agonists, such as tamoxifen, are unable to completely block ER activation



In search of a different mechanism to target the estrogen pathway, AIs were developed in the 1990s to block the synthesis of estrogen and deprive the ER+ tumor of its activating ligand. However, most patients with metastatic breast cancer have been shown to ultimately develop resistance to these therapies. Similar to tamoxifen, resistance to AIs, such as anastrozole, exemestane or letrozole, can develop by multiple mechanisms, including activation of the AF1 pathway and development of mutations. Mutations in ESR1 that confer estrogen-independent ER activity arise in up to 50% of patients receiving treatment with an AI in combination with a CDK4/6 inhibitor in the first-line metastatic setting.

SERDs

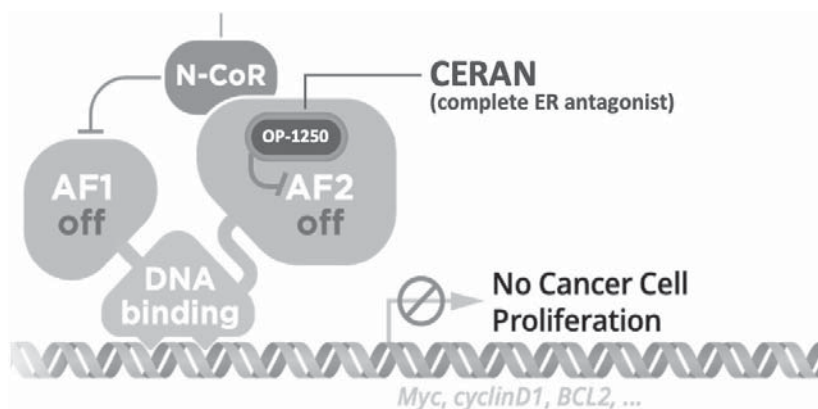
In the search for more potent ER antagonists, researchers focused on another class of ER drugs that were described as SERDs. This classification arose from the observation that certain ligands bind tightly to ER

leading to ER degradation. The field shifted drug discovery efforts to SERDs based on the hypothesis that degrading ER would be more efficacious than inhibiting it. However, similar to tamoxifen, many compounds with SERD activity are not complete ER antagonists nor do they achieve complete degradation of the ER. Recent experiments conducted by us and third parties in nonclinical models of breast cancer suggest that ER degradation, as achieved by many SERDs, on its own is not sufficient to effectively treat tumors and that the ability to completely inhibit ER function is best achieved through complete antagonism.

CERANs

A CERAN is a molecule that completely blocks the ability of both AF1 and AF2 to stimulate gene transcription (Figure 7). CERANs inhibit activation of the AF2 transcription factor activation domain and inactivate AF1 activity by recruiting nuclear receptor corepressors of the N-CoR/SMRT family. Previous work by one of our co-founders identified specific interactions between fulvestrant-bound ER and N-CoR and that the strength of these interactions correlated with the ability of fulvestrant-bound ER to inactivate gene transcription through the transcription factor activating domain, AF1.

Figure 7. Complete antagonists turn off AF2 and recruit N-CoR to inactivate AF1



In 2002, fulvestrant was approved as a treatment for HR+ metastatic breast cancer and is typically used as a second- or third-line endocrine agent. Fulvestrant represented a breakthrough for the field based on its dual-mechanism of action as a CERAN and SERD which led to improved efficacy outcomes for patients. However, fulvestrant, the only FDA-approved anti-estrogen lacking agonist-type effects in *in vivo* uterotrophic assays in immature or ovariectomized mice and rats, has several limitations including:

- Painful and inconvenient route of administration. Fulvestrant is a highly insoluble compound with poor oral bioavailability and therefore must be given intramuscularly. Fulvestrant is administered every 28 days in two 5 ml intramuscular injections into the buttocks. Injection site reactions occur in approximately 10% of patients and include sciatica, neuralgia, neuropathic pain, and peripheral neuropathy.
- Suboptimal drug exposure limits efficacy. In a nonclinical mouse model, an increase in antitumor activity and ER degradation was observed as the dose of fulvestrant was increased from 25 mg/kg to 200 mg/kg. However, researchers estimated that achieving an equivalent level of fulvestrant in humans to a 200 mg/kg dose in mice would require a dose that is eight times higher than is currently clinically achievable. Furthermore, xenograft models created using patient-derived tumors containing ESR1 mutations show that even plasma levels substantially higher than those achievable in humans at the approved dose fail to demonstrate optimal antitumor effect.

Our Product Candidate

We own worldwide development and commercialization rights to OP-1250. Our plan is to develop OP-1250 for the treatment of a number of ER+ breast cancer indications, both as a monotherapy and in combination with approved targeted therapies that have shown improved outcomes with other endocrine therapies.

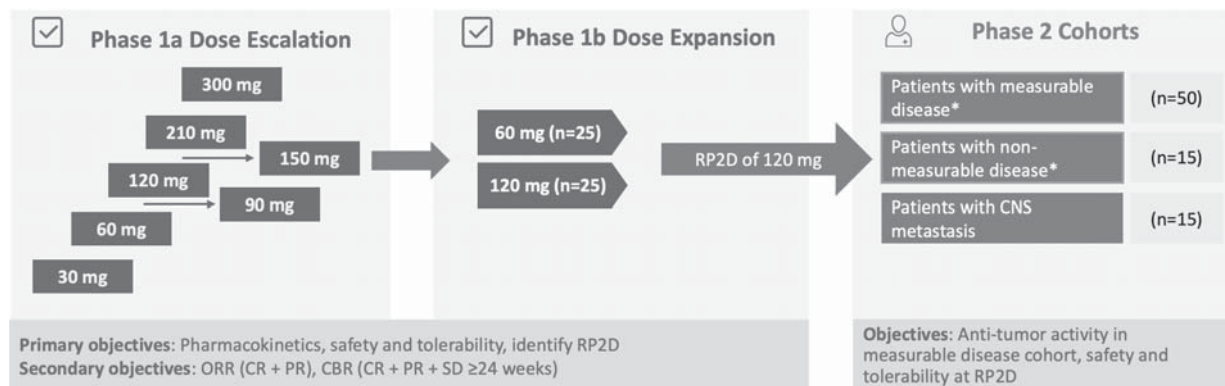
Our solution, OP-1250

OP-1250 is an oral small molecule clinical-stage product candidate for the treatment of endocrine-driven cancers. OP-1250 was designed by our scientific team based both on a detailed structural understanding of the ER and on known alterations to this structure induced by fulvestrant and other ER ligands. We have demonstrated in nonclinical studies that OP-1250 functions both as a CERAN, inactivating both AF1 and AF2 transcriptional activation functions, and a SERD, promoting degradation of the ER. We believe OP-1250's oral formulation and dual mechanism of action directly address the limitations of current endocrine therapies, such as fulvestrant and tamoxifen, and position OP-1250 as a potential endocrine therapy of choice for the treatment of ER+ breast cancers.

Phase 1/2 monotherapy clinical study

Our Phase 1/2 monotherapy clinical development plan for OP-1250 is outlined in Figure 8 below. We initiated the Phase 1a dose escalation portion of our Phase 1/2 monotherapy clinical study in July 2020 and reported initial results across 41 patients in November 2021. In December 2021, we initiated the Phase 1b dose expansion portion of our monotherapy clinical development plan by expanding enrollment at two doses of 60 mg and 120 mg once daily. We enrolled a total of 68 patients across these two doses through the end of July 2022 and reported interim results in October 2022. In the third quarter of 2022, we selected 120 mg as our recommended Phase 2 dose, or RP2D, and initiated enrollment in the Phase 2 portion of our monotherapy study including targeting a total enrollment of 50 patients with measurable disease, 15 patients with non-measurable disease, and 15 patients with CNS metastasis. Our first two primary cohorts of 50 patients with measurable disease and 15 patients with non-measurable disease were fully enrolled in the fourth quarter of 2022.

Figure 8. Design of the Phase 1/2 OP-1250-001 monotherapy study for OP-1250



*Fully-enrolled.

Phase 1a dose-escalation results

We reported the first clinical data from the Phase 1a dose-escalation portion of the ongoing Phase 1/2 clinical study of OP-1250 in November 2021, with a data cut-off of November 1, 2021. These initial data provide proof-

of-concept for OP-1250 as a once-daily oral monotherapy in women with recurrent, locally advanced or metastatic ER+/HER2- breast cancer.

PK, safety, tolerability, and anti-tumor activity of once-daily OP-1250 monotherapy were evaluated in the open-label, dose-escalation portion of the ongoing Phase 1/2 clinical study (NCT04505826). As of November 1, 2021, a total of 41 patients with recurrent, locally advanced or metastatic ER+/HER2- breast cancer were enrolled across seven dose cohorts (30 mg, 60 mg, 90 mg, 120 mg, 150 mg, 210 mg, and 300 mg once-daily). This was a heavily pretreated population with 95% of patients previously treated with a CDK4/6 inhibitor (nine patients, or 22%, received two or more prior CDK4/6 inhibitor regimens), 68% of patients received prior fulvestrant, and 42% received prior chemotherapy in the advanced setting. Overall, patients received a median of three prior lines of anti-cancer therapy and two prior lines of endocrine therapy in advanced settings. Of 39 patients whose circulating tumor DNA, or ctDNA, was assessed, ESR1 mutations were detected in 49% at baseline.

PK analyses demonstrated dose-proportional increases in OP-1250 exposures across all evaluated doses, high oral bioavailability and steady-state plasma levels with minimal peak-to-trough variability. OP-1250 was generally well tolerated, and no dose-limiting toxicities were reported at any of the seven dose levels studied. A maximum tolerated dose was not reached. The majority of reported adverse events were grade 1 or 2 at all dose levels, and the most common treatment-related adverse events, or TRAEs, as assessed by study investigator were nausea (49%), fatigue (34%), vomiting (22%) and headache (17%). No clinically significant bradycardia, ocular toxicities or diarrhea occurred. As of the data cut-off of November 1, 2021, three patients had grade 4 neutropenia attributed to study drug by the investigator. Two of these patients presented with fever and neutropenia. A RP2D range of 60 mg to 120 mg was identified for further evaluation based on PK, favorable tolerability, and initial evidence of anti-tumor activity.

Early evidence of anti-tumor activity was observed in patients across all dose levels tested in the Phase 1a dose escalation portion of the study. Patients were scheduled for tumor assessments at eight-week intervals. Patients were considered efficacy-evaluable for overall response rate, or ORR, if they had response evaluation criteria in solid tumors, or RECIST,-measurable disease at baseline and at least one post-baseline tumor assessment or discontinued treatment prior to their first post-baseline assessment, and for CBR if they were enrolled at least 24 weeks prior to the data cut-off date.

As of the data cut-off date of November 1, 2021, three partial responses were observed among 24 efficacy-evaluable patients, including two confirmed partial responses and one unconfirmed partial response. The patient with the unconfirmed partial response demonstrated robust target lesion reduction of 100% but remained unconfirmed due to progressive disease with a new lesion appearing at a follow-up visit. All three responses occurred in patients with ESR1 mutations and who had previously received CDK4/6 and aromatase inhibitors, and fulvestrant. As of the data cut-off date, 32% of patients (13/41) remained on treatment with efficacy data continuing to mature, including both patients with confirmed partial responses.

Phase 1b/2 monotherapy dose expansion clinical study

We reported interim clinical results from the Phase 1b monotherapy dose expansion portion of the Phase 1/2 study of OP-1250 in October 2022 at a poster session of the 34th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain, with a data cut-off of September 2, 2022. The results continued to demonstrate that at doses of 60 mg and 120mg once daily, OP-1250 is well-tolerated, achieves high drug exposure, and has encouraging anti-tumor activity across both wild-type and ESR1 mutant tumors.

PK, safety, tolerability, and anti-tumor activity of once-daily OP-1250 monotherapy were evaluated in the ongoing Phase 1/2 clinical study (NCT04505826). As of September 2, 2022, 68 patients with recurrent, locally advanced or metastatic ER+/HER2- breast cancer were treated across two doses of 60 mg and 120 mg orally once per day. This group was heavily pretreated with 69% having received 2 or more prior lines of therapy and 32% having received prior chemotherapy in the advanced setting. Almost all patients (96%) received prior treatment with a CDK4/6 inhibitor, and 65% received prior treatment with fulvestrant. Of 46 patients whose ctDNA was assessed, 59% had activating mutations in ESR1 at baseline.

We anticipate presenting Phase 2 clinical data for OP-1250 as a monotherapy in the second half of 2023.

Figure 9. Baseline patient characteristics for OP-1250 monotherapy Phase 1b expansion study

Patient characteristics	60 mg (n=33)	120 mg (n=35)	Total ^a (N=68)
Age, median, years	61	61	61
Range	30–81	39–77	30–81
ECOG performance status, n (%)			
0	22 (67)	17 (49)	39 (57)
1	11 (33)	18 (51)	29 (43)
Measurable disease at baseline, n (%)	32 (97)	34 (97)	66 (97)
Visceral disease (liver, lung, peritoneum, pleura, ascites), n (%)	27 (82)	29 (83)	56 (82)
Prior lines of therapy in advanced setting, n (%)			
1	9 (27)	11 (31)	20 (29)
2	9 (27)	10 (29)	19 (28)
≥3	15 (46)	13 (37)	28 (41)
Missing	0	1 (3)	1 (2)
Prior lines of endocrine therapy in advanced setting, n (%)			
1	13 (39)	12 (34)	25 (36)
2	8 (24)	15 (43)	23 (34)
≥3	11 (33)	7 (20)	18 (27)
Missing	1 (3)	1 (3)	2 (3)
Types of prior therapy in advanced setting, n (%)			
Chemotherapy	14 (42)	8 (23)	22 (32)
AI	26 (79)	29 (83)	55 (81)
Fulvestrant	22 (67)	22 (63)	44 (65)
CDK4/6 inhibitor	32 (97)	33 (94)	65 (96)
ESR1 mutations at baseline (ctDNA), n/N (%)	15/20 (75)	12/26 (46)	27/46 (59)

^aSums may not total to 100% due to rounding.

^{*}Source: EMERALD Phase 3 trial in CDK 4/6 inhibitor-experienced 2/3L patients, Journal of Clinical Oncology.

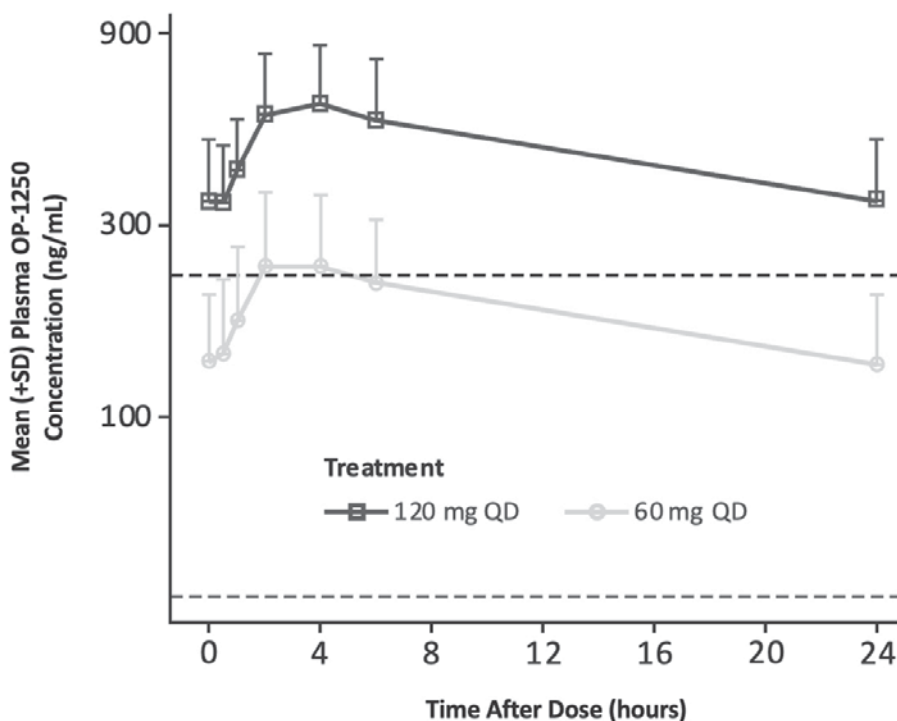
AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ECOG, Eastern Cooperative Oncology Group.

Pharmacokinetics

OP-1250 demonstrated favorable PK characterized by high oral bioavailability and dose proportional exposure. With an approximately 8-day half-life, OP-1250 exhibited the desired low peak-to-trough variability in a 24-hour period at steady state, supporting once daily dosing with complete inhibition of the ER for the full dosing interval.

A RP2D of 120 mg once per day orally was selected based on overall PK, tolerability and efficacy. Dosing at the RP2D yielded drug exposure that exceeded targeted efficacy thresholds based on pre-clinical models.

Figure 10. OP-1250 steady-state plasma concentration-time profiles



Dashed black line=target efficacious exposure based on estradiol-supplemented preclinical models (C_{min} =226 ng/mL) (8 studies); dotted red line=fulvestrant C_{max} =28mg dosed at 500mg every 28 days QD, once daily.

Tolerability

Treatment with OP-1250 was well tolerated at both the 60 mg and 120 mg dose levels with no dose-limiting toxicities. The most common TRAEs that occurred in at least 15% of subjects as assessed by the treating physician were nausea (42%), fatigue (25%) and vomiting (15%). Of the 68 patients treated, one patient experienced Grade 3 neutropenia concurrent with progressive disease, and three patients experienced Grade 4 neutropenia at the 120 mg dose. Of these cases, one patient had dosing interrupted for one week, restarted therapy at 60 mg and subsequently had a confirmed response with no further incidence of neutropenia. The two other patients discontinued treatment with recovery of their neutrophil counts. These events have occurred at a low rate and are manageable and reversible.

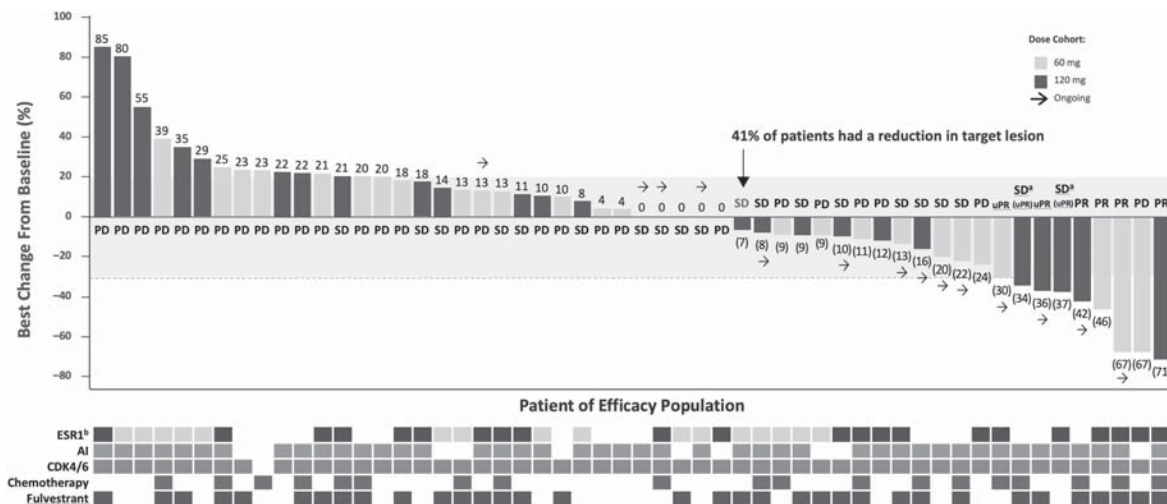
Figure 11. Treatment-related adverse events for OP-1250 monotherapy Phase 1b expansion study

TRAEs in ≥15% of Patients in Phase 1a/1b	60 mg (n=33)			120 mg (n=35)			Total (60 mg & 120 mg, n=68)	
	Grade 1	Grade 2	≥Grade 3	Grade 1	Grade 2	≥Grade 3	Grade 1/2	≥Grade 3
Any TRAE	9	7	1	18	3	6	37 (54%)	7 (10%)
Nausea	8	2	0	18	0	1	28 (41%)	1 (1%)
Fatigue	5	4	0	5	2	1	16 (24%)	1 (1%)
Vomiting	2	1	0	7	0	0	10 (15%)	0

Efficacy

Six partial responses across the two doses had been observed as of the data cut-off date of September 2, 2022 among 57 efficacy-evaluable patients (per RECIST measurable lesions and at least one on-treatment tumor assessment), including four confirmed partial responses and two unconfirmed partial responses awaiting confirmation at a follow-up scan. Strong anti-tumor activity was observed with 41% of patients demonstrating reduction in target lesions and evidence of activity in both wild-type and mutant estrogen receptors across both doses. As of the data cut-off date, 31% of patients (21/68) remained on treatment with efficacy data continuing to mature.

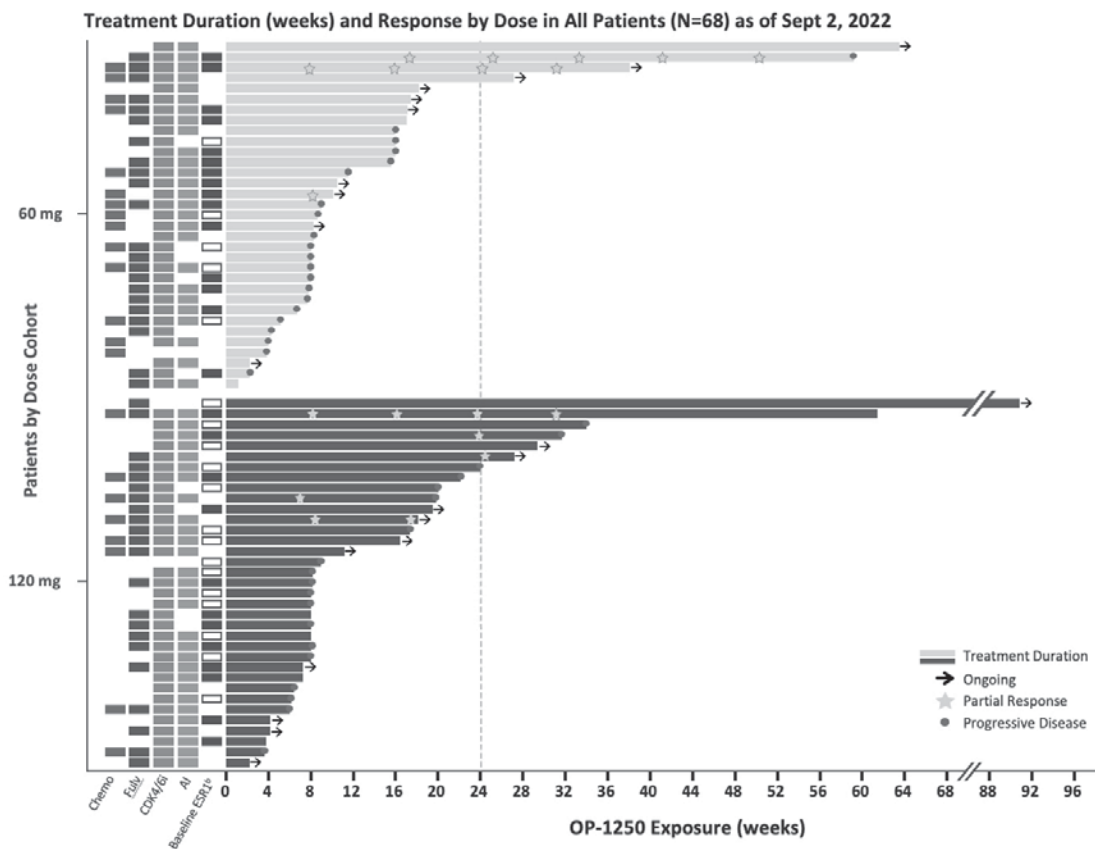
Figure 12: Meaningful anti-tumor activity in OP-1250 Phase 1b dose expansion study



- ^a Patient had an unconfirmed partial response and later progressed at a subsequent scan.
- ^b Dark shaded boxes indicate ESR mutation present, light shaded boxes indicate wild-type, and the absence of a box indicates missing data.

AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; Chemo, chemotherapy; Fulv, fulvestrant; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; uPR, unconfirmed partial response.

Figure 13: Treatment duration and response for OP-1250 Phase 1b monotherapy dose expansion



^bSolid boxes indicate ESR mutation present, open boxes indicate wild-type, and the absence of a box indicates missing data.

*Unconfirmed partial responses awaiting confirmation at a subsequent scan.

AI, aromatase inhibitor; CDK4/6i, CDK4/6 inhibitor; Chemo, chemotherapy; Fulv, fulvestrant; PD, progressive disease; PR, partial response.

Phase 1b/2 combination dose escalation and expansion clinical studies

Our clinical development strategy for OP-1250 includes exploring the potential for combination treatment of advanced or metastatic breast cancer with other targeted therapies. We are initially focused on exploring the potential for OP-1250 in combination with CDK4/6 inhibitors palbociclib and ribociclib and PI3K α inhibitor, alpelisib. In December 2021, we initiated the Phase 1b dose escalation portion of our Phase 1b/2 combination clinical study in combination with palbociclib and reported preliminary results in December 2022. We are currently enrolling patients in the Phase 2 dose expansion portion of this study. We anticipate presenting results from this Phase 2 clinical study in the second quarter of 2023. In the third quarter of 2022, we initiated the Phase 1b dose escalation portion of our Phase 1b/2 combination clinical study in combination with both ribociclib and alpelisib. We anticipate presenting data from the Phase 1b clinical study for OP-1250 in combination with ribociclib in the second half of 2023.

Phase 1b/2 combination dose escalation and expansion clinical study with palbociclib

In December 2021, we initiated a Phase 1b/2 clinical study of OP-1250 in combination with palbociclib, a CDK4/6 inhibitor. We reported preliminary clinical data from the Phase 1b dose escalation portion of the clinical study in December 2022 at the 2022 San Antonio Breast Cancer Symposium in San Antonio, Texas. The preliminary results demonstrated attractive combinability with no dose-limiting toxicities, no dose-related increase in the incidence or severity of adverse events and no DDI with exposure levels of each drug consistent with monotherapy or standard of care combinations.

As of the data cut-off of September 12, 2022, 12 patients with recurrent, locally advanced or metastatic ER+/HER2- breast cancer were treated across four dose escalation cohorts: three patients per cohort dosed at 30, 60, 90, and 120 mg in combination with palbociclib 125 mg. Ten of the 12 patients received prior therapy for advanced disease, including eight patients who had received prior CDK4/6 inhibitors and nine patients who received prior endocrine therapy for advanced disease. Of 11 patients whose ctDNA was assessed, 36% had activating mutations in ESR1 at baseline.

Figure 14. Baseline patient characteristics from Phase 1b study in combination with palbociclib

Patient characteristics	Total^a (N=12)
Median age (years)	62
Range	49–76
ECOG performance status, n (%)	
0	9 (75)
1	3 (25)
Measurable disease at baseline, n (%)	11 (92)
Visceral disease (liver, lung, peritoneum, pleura, ascites), n (%)	6 (50)
Prior lines of therapy in advanced setting, n (%)	
0	2 (17)
1	7 (58)
2	2 (17)
3	1 (8)
Prior lines of endocrine therapy in advanced setting, n (%)	
0	3 (25)
1	9 (75)
Types of prior therapy in advanced setting, n (%)	
Chemotherapy	3 (25)
Aromatase inhibitor (AI)	8 (67)
Fulvestrant	1 (8)
CDK4/6 inhibitor	8 (67)
ESR1 mutations at baseline (ctDNA), n/N (%)	4 (36); N=11 evaluated

Pharmacokinetics

OP-1250 demonstrated favorable PK characterized by high oral bioavailability, dose proportional exposure and a long half-life of eight days, with steady-state plasma levels showing minimal peak-to-trough variability, enabling consistent inhibition of ER for the full dosing interval. There was no observed DDI between palbociclib and OP-1250 in the dose range of 30 mg to 120 mg. Palbociclib did not affect OP-1250 drug exposures compared to monotherapy dosing, and OP-1250 had no effect on palbociclib 125 mg drug exposures when compared to published concentrations.

Figure 15. Steady state C_{max} of OP-1250 combination vs. single agent

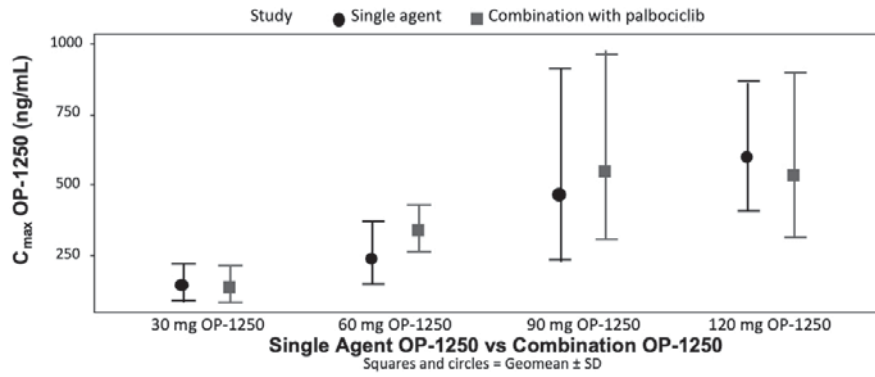


Figure 16. Steady state $AUC_{(0-24)}$ of OP-1250 combination vs. single agent

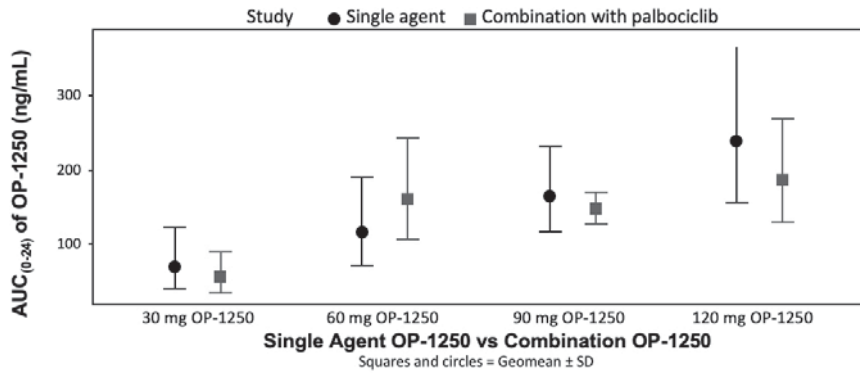
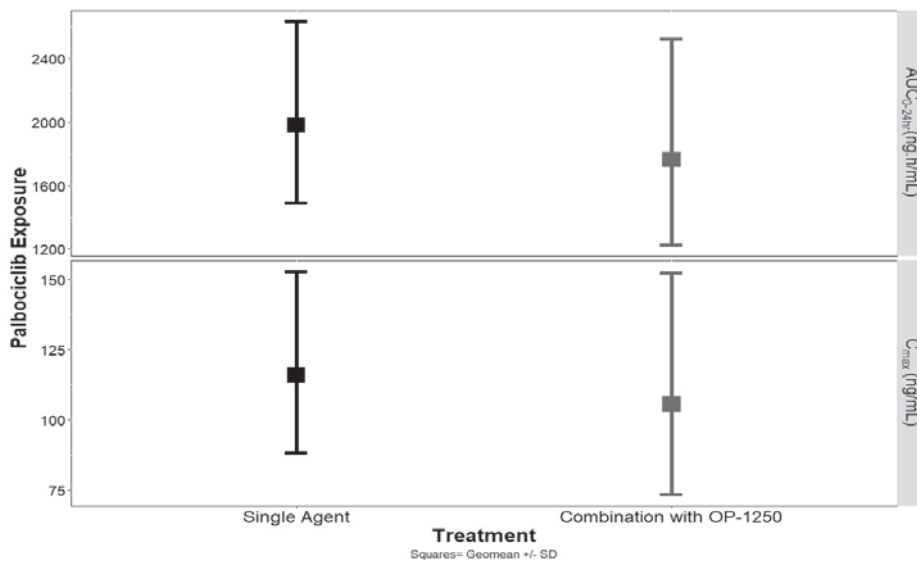


Figure 17. Steady state AUC_{0-24} and C_{max} of palbociclib vs. published concentrations



Tolerability

Treatment with OP-1250 up to the RP2D of 120 mg was well tolerated with no dose-limiting toxicities, and maximum tolerated dose, or MTD, was not reached. The majority of treatment-emergent adverse events, or TEAEs, were Grade 1 or 2 and increasing the dose did not show an increase in frequency of events. OP-1250 was not dose-reduced in any patients, and no patients discontinued treatment with OP-1250 due to an adverse event, including neutropenia. Neutropenia events observed were consistent with the expected profile of palbociclib plus an endocrine therapy. There was no Grade 4 neutropenia, and eight of 12 patients reported Grade 3 neutropenia, a rate which is consistent with the FDA-approved label of palbociclib plus an endocrine agent.

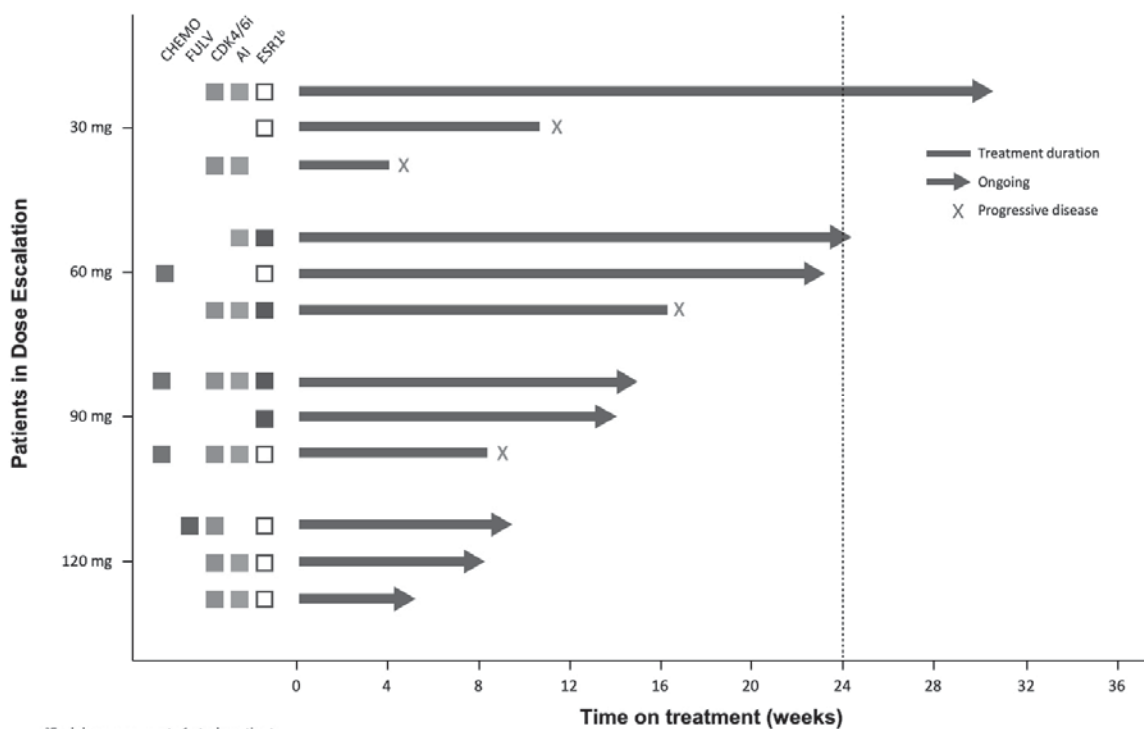
Figure 18. Treatment-emergent adverse events for OP-1250 in combination with palbociclib

TEAEs in ≥15% of Patients	Total (N=12)			
	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia ^a	1	2	8	0
Nausea	3	3	0	0
Vomiting	5	0	0	0
Anemia	2	2	0	0
GERD	2	2	0	0
Constipation	2	1	0	0
Fatigue	2	0	1	0
Thrombocytopenia	3	0	0	0
COVID-19	0	2	0	0
Decreased appetite	1	1	0	0
Diarrhea	0	2	0	0
Headache	2	0	0	0
Sinus bradycardia	1	1	0	0
UTI	0	2	0	0
WBC count decreased	0	1	1	0

^a Includes adverse events reported as either "Neutropenia" or "Neutrophil count decreased."

TEAE, Treatment-Emergent Adverse Event. UTI, urinary tract infection, WBC, white blood cell
Data Cutoff Date: September 12, 2022

Figure 19. Treatment duration and response for OP-1250 Phase 1b in combination with palbociclib



^aEach lane represents 1 study patient.

^bSolid boxes indicate ESR mutation present, open boxes indicate wild-type, and the absence of a box indicates missing data.

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CHEMO, chemotherapy; ESR1, estrogen receptor 1; FULV, fulvestrant.

Clinical development plan for OP-1250 and additional clinical opportunities

In the third quarter of 2022, we selected 120 mg once daily as the RP2D. We completed enrollment in the two primary cohorts of our Phase 2 monotherapy expansion study in the fourth quarter of 2022 (50 patients with measurable disease and 15 patients with non-measurable disease) at the RP2D. Based on our clinical results to date, we are actively planning to initiate a monotherapy pivotal Phase 3 trial in the second half of 2023 in the second- and third-line setting for locally advanced or metastatic ER+/HER2- breast cancer, subject to feedback from the FDA and EMA.

We are currently exploring the potential for OP-1250 to combine with CDK4/6 inhibitors palbociclib and ribociclib in Phase 1b/2 dose escalation and expansion studies. Subject to positive results from these ongoing studies, we anticipate initiating a pivotal Phase 3 clinical trial in combination with a CDK4/6 inhibitor in 2024 for the treatment of advanced or metastatic ER+/HER2- breast cancer in the first-line setting.

While all populations described above are in patients with ER+/HER2- breast cancer, we believe that there is an opportunity for us to study OP-1250 in patients with ER+/HER2+ breast cancer, which represents approximately 11% of breast cancer patients and more than 50% of the patients with HER2+ breast cancer. In particular, up to 50% of patients with metastatic HER2+ breast cancer develop CNS disease. We believe that combining OP-1250 with HER2 targeted agents may represent an opportunity to improve upon recent advancements in the treatment of CNS disease in patients that express both ER and HER2.

We are conducting a series of pharmacology studies for OP-1250, including DDI fed/fast and bioequivalence to a tablet formulation, and expect to complete these studies in 2023. We believe that the conversion from

capsule to tablet formulation of OP-1250 may have certain clinical advantages and we expect to transition to tablet administration prior to initiation of a pivotal trial in what we expect to be the second half of 2023.

While our initial studies are focused on treating breast cancer patients with metastatic disease, we believe that if OP-1250 is determined to be safe and effective in this population, there is potential for it to be used in earlier stage disease. Based on our extensive nonclinical studies, including certain head-to-head studies, we believe that OP-1250 could have superior PK properties and improved clinical outcomes than fulvestrant. If proven in the clinic, we believe that OP-1250 has the potential to not only replace fulvestrant but to become the endocrine treatment of choice for the treatment of both advanced/metastatic ER+ breast cancer as well as ultimately in early-stage ER+ breast cancer in the adjuvant setting.

In addition to breast cancer, we intend to explore the use of OP-1250 in various gynecological malignancies, beginning with endometrial cancer. Approximately 80% of endometrial tumors are “endometrioid” in nature and these tumors are driven by estrogen.

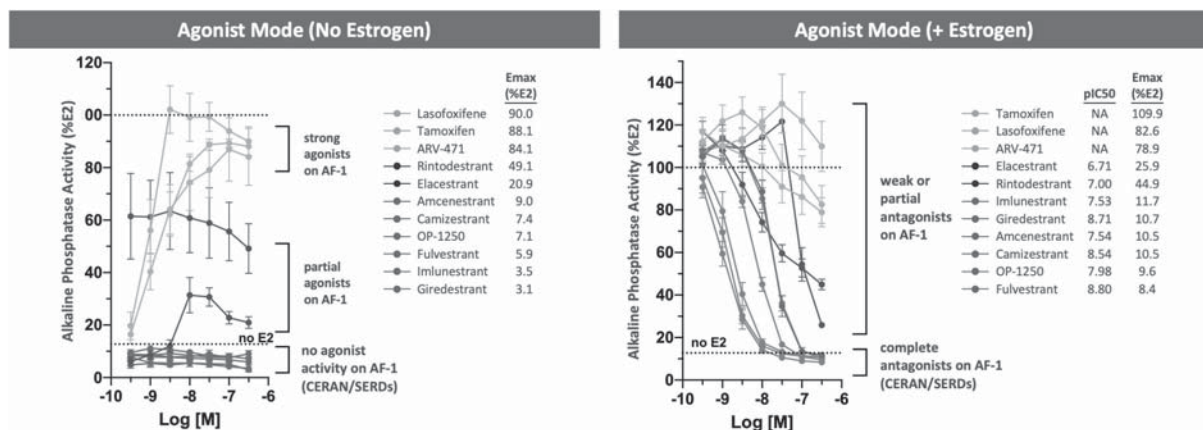
Nonclinical data

Complete ER antagonism

A key distinguishing feature of CERANs is that they completely lack any agonistic estrogen-like effects, and completely block the effects of estrogen. In a nonclinical model, we evaluated OP-1250 and other compounds with publicly-disclosed chemical structures that have been or are in clinical development for ER+ breast cancer to compare their ability to block breast cancer proliferation and degrade estrogen receptors. Alkaline phosphatase, or AP, is an estrogen-responsive gene in ECC-1 cells driven by AF1 action. The *in vitro* AP model is a method of determining complete ER antagonism. As shown in Figure 20 below, OP-1250 and other CERANs lack agonistic estrogen like effects and completely block the effects of estrogen.

In the absence of estrogen, OP-1250 and other CERANs completely inactivated AF1 and did not stimulate AF1-dependent AP activity. In the presence of estrogen, OP-1250 and other CERANs demonstrated complete antagonism while non-CERANs were unable to fully inhibit estrogen-stimulated AF-1 activity.

Figure 20. CERANs do not activate AF1 in the absence of estrogen, and partial and strong agonists do not fully inhibit estrogen-stimulated AF-1 activity

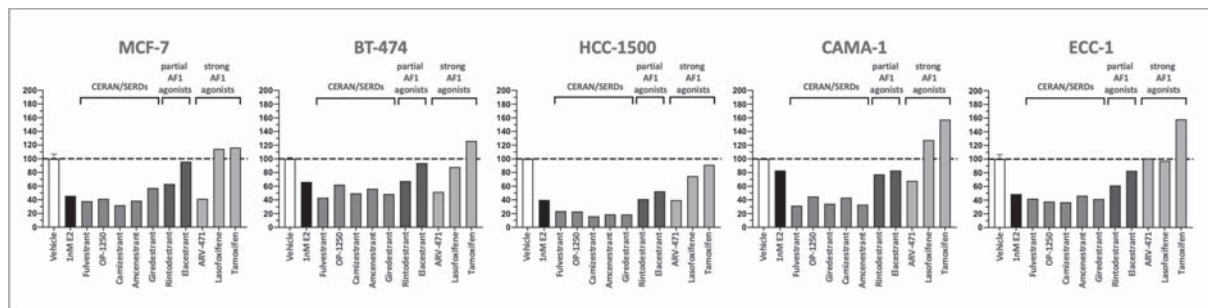


SERD activity

SERDs are ER ligands that lead to partial degradation of the ER. This degradation takes place within four hours after exposure of cells to the SERD, indicating that it comes from destabilization of the ER protein. In a

nonclinical analysis, we have tested the ability of OP-1250, fulvestrant, other CERANs and several non-CERAN SERDs to degrade ER across five different cell lines. As shown in Figure 21, after treatment of these cell lines for four hours, OP-1250 and other CERANs strongly degraded the estrogen receptor in all five ER+ cell lines, while non-CERANs demonstrated variable and inconsistent ER degradation. Of note, Estradiol, or E2, the prototypical agonist of ER α , degraded ER α in all five ER+ cell lines. In all cases, none of the compounds achieved full ER degradation, further supporting our belief that complete ER antagonism is independent from degradation and key to inactivating any remaining ER receptor.

Figure 21. CERAN/SERDs and SERM/SERDs are strong degraders of ER α across multiple cell lines

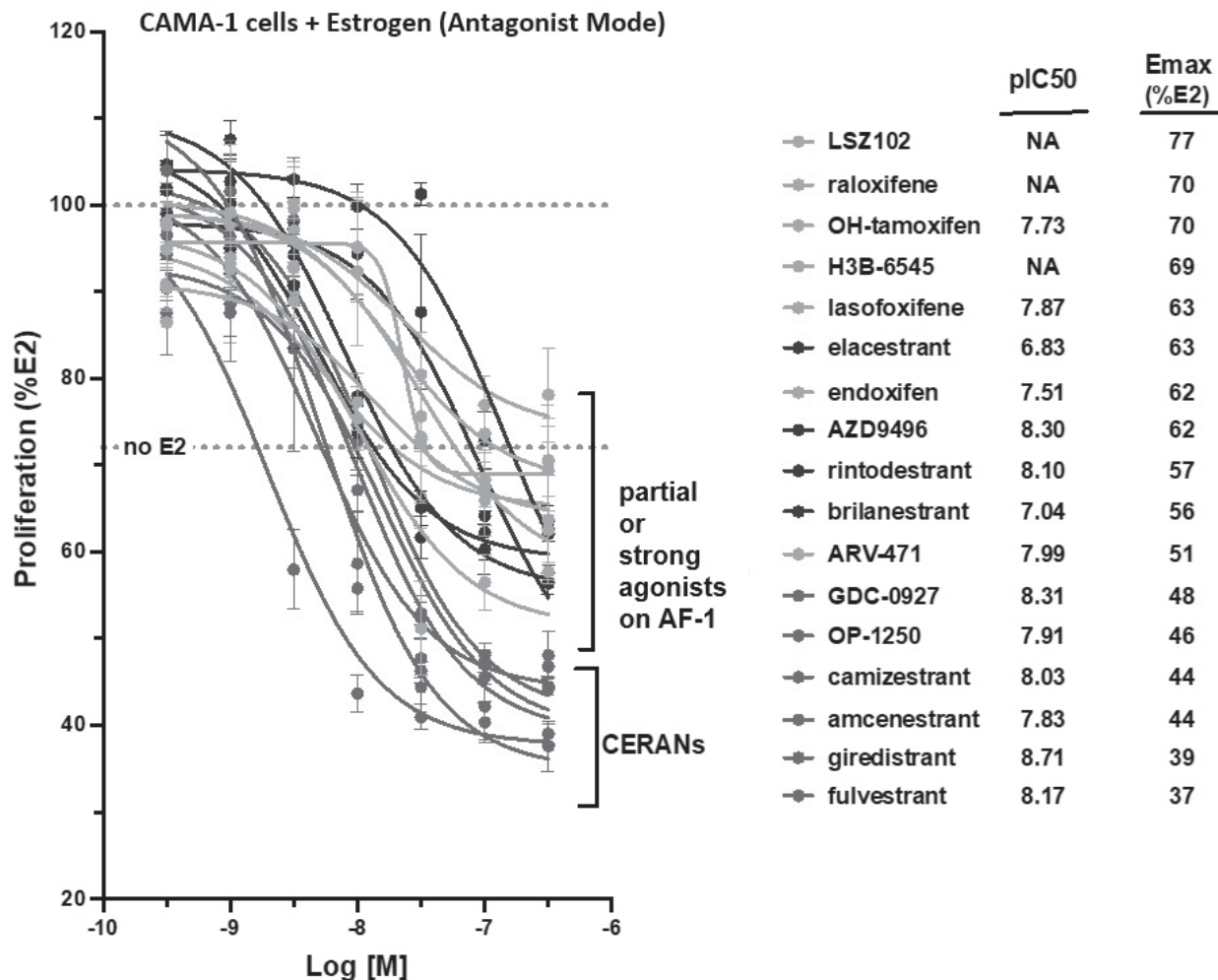


Immunoblot of ER α across multiple ER+ cell lines. Cells were incubated with 300nM compounds for 4h in estrogen-depleted media. Shown here are the densitometry results of the immunoblot showing ER α protein levels relative to vehicle-treated cells after normalizing ER α to actin.

Potent anti-proliferative activity

In nonclinical studies, we found that OP-1250 was a potent inhibitor of proliferation in multiple breast cancer cell lines. As shown in Figure 22 below, in a cell proliferation assay using CAMA-1 cells, a human breast cancer line, OP-1250 and other CERANs inhibited estrogen-driven proliferation to a greater degree than non-CERANs.

Figure 22. OP-1250 and CERANs more completely block estrogen-driven breast cancer proliferation than non-CERANs



Proliferation of CAMA-1 breast cancer cells treated with antiestrogens for 6-8 days in the presence of 100pM E2 in E2-depleted media. Cell number was approximated using a DNA-binding dye. Shown are mean values normalized to E2 from 3 independent experiments.

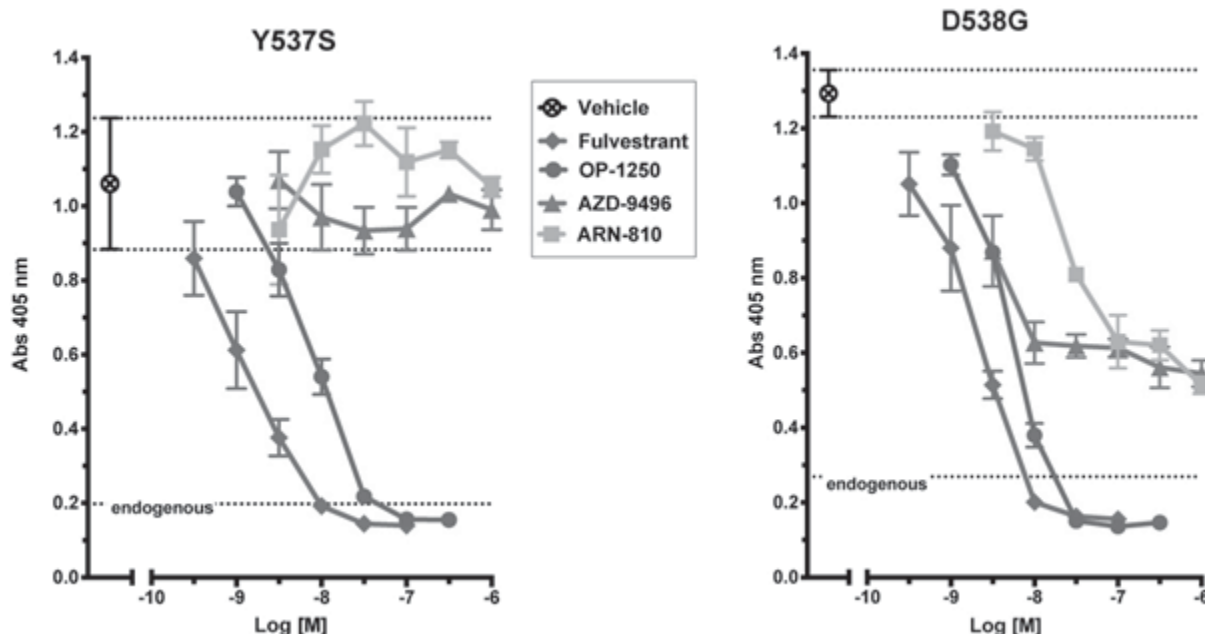
Potent antagonist activity on both wild-type and mutant ER

Treatment of breast cancers with AI therapy has been shown to lead to the development of resistance mutations in the ESR1 gene. These mutations are acquired during treatment and are found in less than 2% of untreated early-stage breast tumors but in 30-40% of metastatic tumors after treatment with AIs. More than 80% of mutations are found at three locations corresponding to amino acid residues 380, 537 and 538.

These mutations result in resistance to many estrogen therapies. We assessed the ability of estrogen compounds to inhibit ER-dependent transcription in cell lines containing ER alleles with mutations that have been found in patients. We used alkaline phosphatase, which is encoded by a gene activated by the ER primarily through the AF1 transcriptional activation function and has an enzymatic activity that can be readily measured in cells, as a surrogate for ER driven target gene transcription. We tested two clinical stage SERD compounds: ARN-810, also known as GDC-0810, a discontinued compound previously in Phase 2 clinical development by Genentech; and AZD9496, an AstraZeneca compound that has presented Phase 1 data. Both

compounds were unable to fully inhibit the activity of the mutant ER. At the highest concentrations tested of approximately 1 μ M, these compounds were unable to fully inhibit the alkaline phosphatase activity stimulated by the D538G mutation and had no activity in cells containing the Y537S mutation. In contrast, both OP-1250 and fulvestrant were able to fully inhibit the alkaline phosphatase activity in cells containing these mutations. These observations suggest that tumors that become resistant to other estrogen therapies may remain sensitive to OP-1250.

Figure 23. Both OP-1250 and fulvestrant inhibit the activity of the ER containing mutations that commonly arise in breast cancer patients treated with other antiestrogen therapies

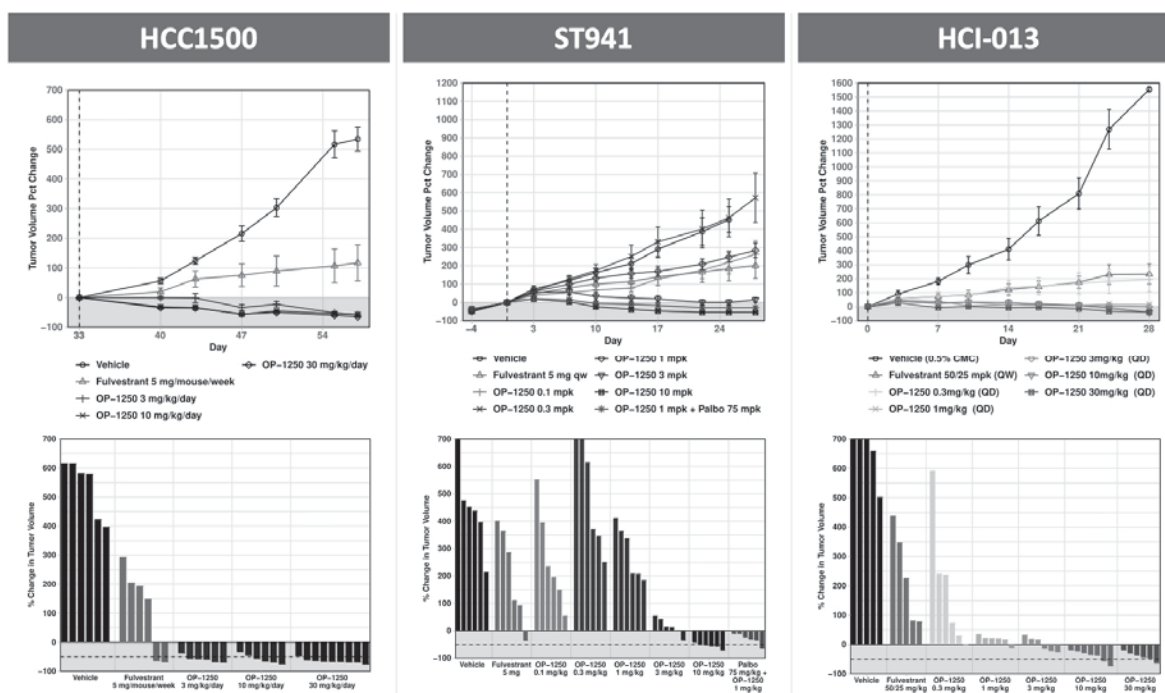


AP activity mediated by Y537S and D538G mutant ER α in an endometrial cell line. AP activity was assayed by treating transiently transfected Ishikawa cells with ligands in E2-depleted media for 3 days. Absorbance was read after incubation with a chromogenic substrate for AP. Shown are mean values normalized to vehicle, along with SEM from triplicate wells. The line labeled "endogenous" represents the mean AP activity of cells transfected with an empty vector, indicating the AP activity of the endogenous receptor. ARN-810, also known as GDC-0810, has been discontinued by Genentech.

Potent tumor shrinkage in nonclinical models

OP-1250 shrank or eliminated tumors in a wide variety of xenograft models including in an ovariectomized mouse breast cancer model designed to mimic the endocrine environment of post-menopausal women using HCl- 013E1, an estrogen-independent patient-derived xenograft model containing a Y537S mutation. In this model, tumor growth occurred even in the absence of estrogen production due to the constitutive or always-on activity of the Y537S mutant ER protein. At daily oral doses of 3 mg/kg and higher, dosing with OP-1250 led to tumor reductions in all treated mice. In contrast, fulvestrant led to a detectable reduction in only two of the seven treated mice.

Figure 24. OP-1250 has demonstrated robust tumor shrinkage in both ESR1 wild-type and mutant xenograft models



Change in tumor volume of HCI013E1 patient-derived tumors, carrying the Y537S mutation in the ER and adapted to grow without estrogen, implanted in the mammary fat pad of non-obese diabetic, or NOD/SCID ovariectomized mice. Mice were treated with oral OP-1250 at the dose indicated, or with subcutaneous fulvestrant (Faslodex preparation). Bottom panel shows tumor size of each tumor measured with calipers at termination. Top panel shows mean tumor size of each treatment group of 8 over the course of the study.

Change in tumor volume of various human xenograft tumors implanted in the mammary fat pad of ovary intact immunodeficient mice supplemented with estrogen releasing pellets and treated with the indicated dose of oral OP-1250, oral OP-1250 plus oral palbociclib, or subcutaneous fulvestrant (Faslodex preparation). Bottom panel of Figure 24 shows tumor size of each tumor measured with calipers at termination. Top panel shows mean tumor size of each treatment group of eight over the course of the study. HCC1500, wild type ER cell line implanted in NSG mice; ST941 patient derived xenograft, or PDX, model with Y537S ER in JAX nude mice; HCI013 PDX model with Y537S ER in NOD/SCID mice.

Daily oral dosing with OP-1250 led to tumor shrinkage in multiple xenograft models in mice with intact ovaries. These models included the HCC1500 cell line, which have wild-type ER and the ST941 and HCI-013 patient-derived xenograft models, both of which contain ERs that have the Y537S mutation. Similar to what was seen in the ovariectomized mouse model, OP-1250 demonstrated more potent antitumor activity than fulvestrant, which failed to consistently shrink tumors in any of these models.

Brain penetration

There remains an unmet medical need in the treatment of patients with metastatic ER+/HER2- breast cancer that has spread to the brain. The challenges in treating brain metastasis are multifactorial and likely include the presence of resistance mutations and the inability to achieve efficacious levels of effective drugs in brain tissue. In mice, we found that OP-1250 reached drug levels in the brain as high as 50% greater than in plasma. Combined with the ability to achieve higher drug levels with OP-1250, due to its improved PK properties, than

fulvestrant, we found that we could obtain brain exposure to concentrations of OP-1250 that were greater than 30 times that of fulvestrant.

Figure 25. OP-1250 demonstrated robust CNS penetration in the mouse brain

Treatment	Dose (mg/kg)	Brain Concentration (ng/g)	Plasma Concentration (ng/mL)	Brain to Plasma Ratio
OP-1250	1	5	10	0.4
OP-1250	3	45	54	0.8
OP-1250	10	499	344	1.4
OP-1250	30	1,920	1,226	1.6
Fulvestrant	50/25	60	69	0.9

OP-1250 was dosed daily orally by gavage in the mouse. Plasma levels were measured by HPLC. Cranial tissue samples removed surgically, weighed, macerated, and extracted to determine the concentration of OP-1250.

OP-1250 was effective in an intracranial xenograft brain metastasis model, in which ST941 tumor cells expressing mutant ESR1-Y537S receptors were implanted directly into the brain by stereotactic surgery. Tumors were stimulated with estrogen and allowed to grow for two or three weeks and their presence in the brain confirmed by MRI. The mice were then treated with one of the following: vehicle control; vehicle control with ovariectomy; 5 mg/mouse fulvestrant; 60 mg/kg tamoxifen; 10 mg/kg OP-1250; or 10 mg/kg OP-1250 in combination with 75 mg/kg ribociclib, a CDK4/6 inhibitor known to cross the blood brain barrier. Mice were treated once daily for up to 100 days and followed for tumor size with MRI and survival.

As shown in the figures below, OP-1250 shrank tumors in a preclinical intracranial xenograft metastatic tumor model expressing mutant estrogen receptor ESR1-Y537S. All tumors responded to OP-1250 treatment. At 100 days, tumors in mice treated with 10 mg/kg OP-1250 or the combination of 10 mg/kg OP-1250 and 75 mg/kg ribociclib remained small or undetectable while tumors in mice treated with fulvestrant and tamoxifen had started to grow. Further, treatment with OP-1250 alone or in combination with ribociclib prevented death in all animals at day 120 while the vast majority of untreated animals died by day 25. We believe that the ability of OP-1250 to eradicate brain metastasis in mice demonstrates that OP-1250 may have the potential to advance the treatment of patients with breast cancer with brain metastases.

Figure 26: Treatment with 10 mg/kg OP-1250 was superior to tamoxifen, fulvestrant and ovariectomy in shrinking mutant ESR1-Y537S tumors in an intracranial model of ER+ breast cancer brain metastasis

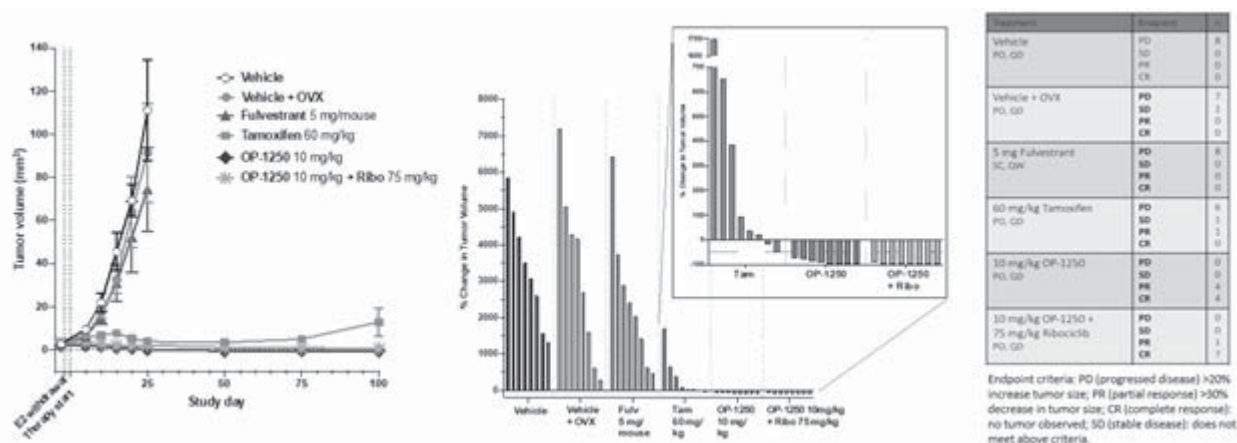
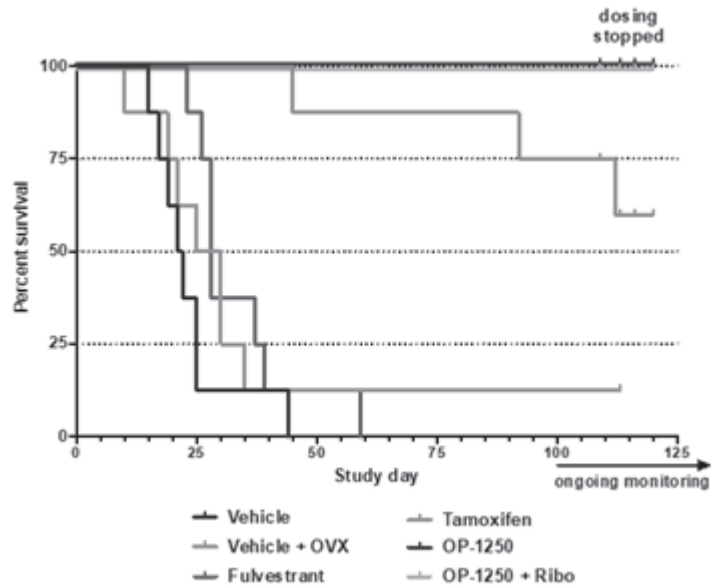


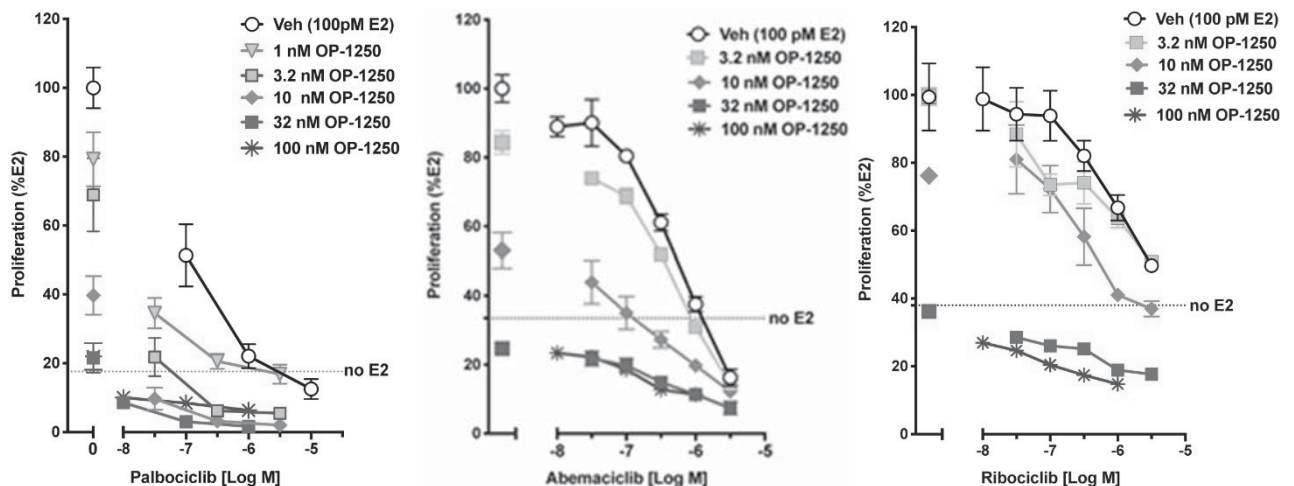
Figure 27. Treatment with OP-1250 led to long-term survival in a xenograft model of breast cancer brain metastases



Combinations with other breast cancer therapies

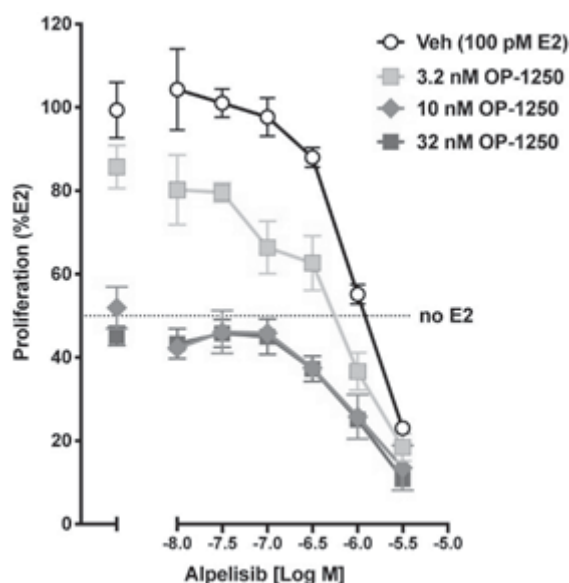
As in most other solid tumors, effective antitumor activity often requires the use of combination therapy. In the case of ER+ breast cancer, for example, activation of the CDK4/6 pathway is associated with resistance to fulvestrant and CDK4/6 inhibitors are routinely used in combination with fulvestrant. We observed that OP-1250 in combination with three different CDK4/6 inhibitors resulted in increased inhibition of MCF-7 cell proliferation as did OP-1250 in combination with the PI3K α inhibitor alpelisib in T47D cells.

Figure 28. The combination of OP-1250 and CDK4/6 inhibitors resulted in potent anti-proliferative activity in MCF-7 cells



In vitro cell proliferation experiment measuring DNA content after 7-day treatment of MCF-7 breast cancer cells with ligands in the presence of 100 pM E2. Shown are mean values normalized to vehicle (+E2), along with SEM from triplicate wells.

Figure 29. The combination of OP-1250 and PI3K α inhibitors resulted in potent anti-proliferative activity in T47D cells

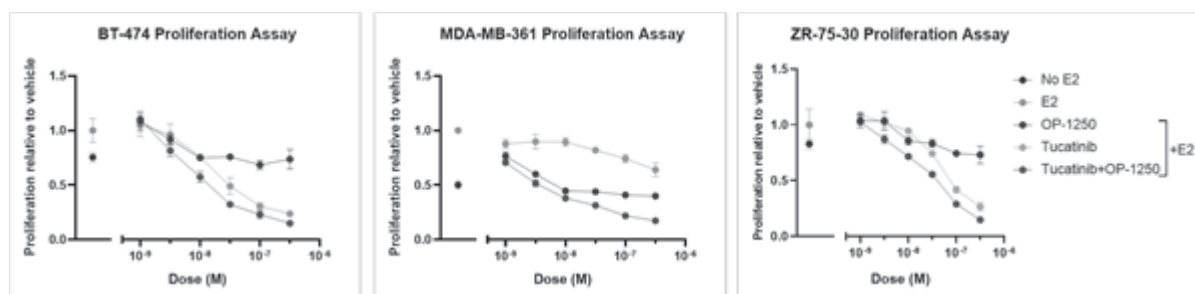


In vitro cell proliferation experiment measuring DNA content after 6-day treatment of T47D breast cancer cells with ligands in the presence of 100 pM E2. Shown are increasing concentrations of alpelisib with three different concentrations of OP-1250, mean values normalized to vehicle (+E2), and SEM from triplicate wells.

ER+/HER2+ breast cancer

In addition to the favorable efficacy profile of OP-1250 in the Phase 1a dose-escalation portion of the ongoing Phase 1/2 clinical study of OP-1250 for the treatment of ER+/HER2- breast cancer, we have shown that OP-1250 can also function in combination with HER2 inhibition in ER+/HER2+ breast cancer cell lines and patient-derived xenograft models. The HER2 oncogene is overexpressed in approximately 25% of breast cancer tumors, about half of which also express ER, and HER2+ tumors have a high rate of brain metastasis. In three ER+/HER2+ cell lines, treatment with OP-1250 reversed the increase in cellular growth induced by treatment with E2 and combined effectively at some dose ranges with the HER2 inhibitor tucatinib.

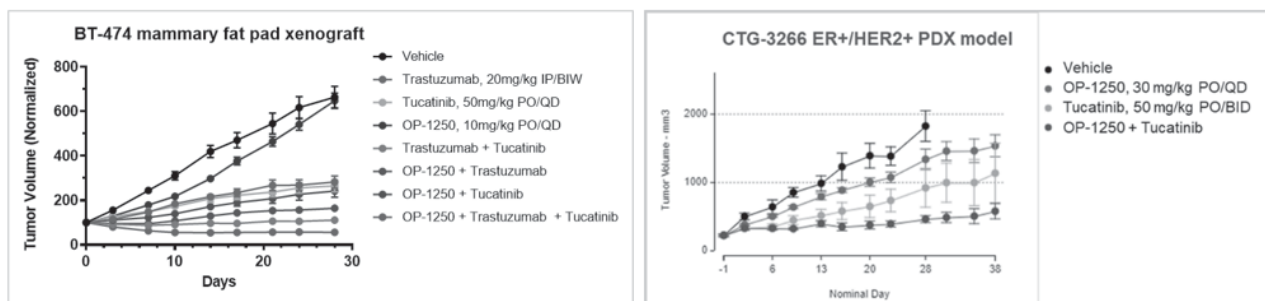
Figure 30. OP-1250 inhibits estrogen receptor-driven proliferation in ER+/HER2+ breast cancer cell lines



Proliferation assays of three ER+/HER2+ cell lines treated for 7 days with OP-1250, tucatinib, or the equimolar combination in stripped serum media supplemented with 500 pM estradiol. All cell lines demonstrate reduction in proliferation with OP-1250 treatment and efficacy of combined compound treatment.

OP-1250 also reduced growth of ER+/HER2+ cell lines or patient-derived xenograft models in mouse xenograft studies. Cells were implanted either subcutaneously or in the mammary fat pad and allowed to establish a tumor prior to dosing with OP-1250 and/or HER2 inhibitors tucatinib and trastuzumab. OP-1250 treatment demonstrated reduced tumor growth in combination with both individual HER2 inhibitors and dual HER2 therapy using both tucatinib and trastuzumab.

Figure 31. The addition of OP-1250 to HER2 inhibitors Tucatinib and Trastuzumab enhances tumor growth inhibition in ER+/HER2+ cell line or patient-derived xenograft models



Xenograft studies of ER+/HER2+ cell line or patient-derived xenograft (PDX) treated with OP-1250 and HER2 inhibitors. Left, tumor volume of BT-474 cell line implanted into the mammary fat pad of NSG mice. Right, tumor growth of CTG-3266 PDX model implanted subcutaneously into nude mice. OP-1250 treatment inhibited growth in both models in combination with HER2 inhibitors. Animals were dosed orally with OP-1250 and tucatinib, and by intraperitoneal injection with trastuzumab at the doses listed.

Summary of nonclinical properties

We believe OP-1250's oral formulation and dual mechanism of action directly address the limitations of current endocrine therapies, such as fulvestrant and tamoxifen, and position OP-1250 as a potential endocrine therapy of choice for the treatment of ER+ breast cancers. We have demonstrated in nonclinical studies that OP-1250 functions both as a CERAN and a SERD, but is distinguished from fulvestrant in several noteworthy ways, including:

- OP-1250 has favorable biodistribution properties leading to higher drug concentrations in the plasma and tumor than those achieved with fulvestrant, as shown in a head-to-head mouse xenograft study; and
- OP-1250 has demonstrated the ability to shrink tumors in head-to-head nonclinical studies with fulvestrant, in contrast to fulvestrant, which has only been shown to inhibit tumor growth.

We believe OP-1250 has the potential to improve clinical outcomes for patients with metastatic breast cancer, initially for patients who have previously received endocrine therapy, as well as those who are treatment naïve in the metastatic setting. Additionally, given the differentiated product profile, we believe that OP-1250 has the potential to advance into the adjuvant setting for early-stage ER+ breast cancer.

Clinical Trial Collaboration and Supply Agreement with Novartis

In July 2020, we entered into a non-exclusive Clinical Collaboration and Supply Agreement, or the Novartis Agreement, with Novartis. The collaboration is focused on the evaluation of the safety, tolerability and efficacy of OP-1250 in combination with Novartis' proprietary CDK4/6 inhibitor KISQALI® (ribociclib) and/or Novartis' proprietary phosphatidylinositol 3-kinase inhibitor PIQRAY® (alpelisib), or collectively the Novartis Study Drugs, as part of our planned Phase 1b clinical study of OP-1250 in patients with metastatic ER+ breast cancer. We

will be responsible for the conduct of the clinical studies for the combined therapies in accordance with a mutually agreed development plan. As part of the collaboration, the parties granted to each other a non-exclusive, royalty- free license under certain of the parties' respective background patent rights and other technology to use the parties' respective study drugs in research and development, solely to the extent reasonably needed for the other party's activities in the collaboration. All inventions and data developed in the performance of the clinical studies for the combined therapies (other than those specific to each component study drug), will be jointly owned by the parties.

We are responsible for manufacturing, packaging and labeling OP-1250, and for packaging and labeling all drugs used in the clinical studies for the combined therapies (other than the Novartis Study Drugs). Novartis is responsible for manufacturing and delivering to us the Novartis Study Drugs in such quantities as reasonably needed for the clinical studies for the combined therapies. In accordance with an agreed budget, Novartis will reimburse us for a majority of the direct outside costs, but no more than an amount in the low single digit millions of U.S. dollars, that we incur related to conducting the activities under the agreed development plan in conducting the clinical trials for the combined therapies.

The Novartis Agreement will terminate upon completion of all activities outlined in the development plan and the relevant protocols. Either party may terminate the Novartis Agreement for the uncured material breach or insolvency of the other party, if it reasonably deems it necessary in order to protect the safety, health or welfare of subjects enrolled in the clinical studies for the combined therapies due to the existence of a material safety issue, or in certain circumstances for an unresolved clinical hold with respect to either the Novartis Study Drugs or OP-1250. In addition, Novartis may terminate the Novartis Agreement if certain disputes between the parties are not resolved after following the applicable dispute resolution procedures, and we may terminate the Novartis Agreement in the event we terminate all clinical studies of the combined therapies other than due to a material safety issue or upon a clinical hold.

The Novartis Agreement does not grant any right of first negotiation to participate in future clinical trials, and each of the parties retains all rights and ability to evaluate their respective compounds in any studies or clinical trials, either as a monotherapy or in combination with any other product or compound, in any therapeutic area. The parties retain their independent rights to commercialize their respective therapies both alone or with other parties.

Clinical Trial Agreement with Pfizer

In November 2020, we entered into a non-exclusive clinical trial agreement with Pfizer, or the Pfizer Agreement, to evaluate the safety and tolerability of OP-1250 in combination with Pfizer's proprietary CDK4/6 inhibitor IBRANCE® (palbociclib) in patients with recurrent, locally advanced or metastatic ER+/HER2- breast cancer in a clinical trial. Under the terms of the non-exclusive agreement, we will be responsible for conducting the clinical study for the combined therapies and Pfizer is responsible for supplying IBRANCE® to us at no cost to us. As part of the collaboration, the parties granted to each other a non-exclusive, royalty- free license under certain of the parties' respective patent rights in the combination of IBRANCE® and OP-1250 to use the parties' respective study drugs in research and development, solely to the extent reasonably needed for the other party's activities in the collaboration. All inventions and data developed in the performance of the clinical trials for the combined therapies (other than those specific to each component study drug), will be jointly owned by the parties.

We are responsible for manufacturing, packaging and labeling OP-1250, and for packaging and labeling all drugs used in the clinical trials for the combined therapies (other than IBRANCE® (palbociclib)). Pfizer is responsible for manufacturing and delivering to us IBRANCE® (palbociclib) in such quantities as reasonably needed for the clinical studies for the combined therapies.

The Pfizer Agreement will terminate upon completion of all activities outlined in the study plan and the relevant protocols. Either party may terminate the Pfizer Agreement for the uncured material breach or insolvency of the other party, if it reasonably deems it necessary in order to protect the safety, health or welfare of subjects

enrolled in the clinical studies for the combined therapies due to the existence of a material safety issue, or in certain circumstances for an unresolved clinical hold with respect to either the IBRANCE® (palbociclib) or OP-1250. In addition, either party may terminate the Pfizer Agreement if certain disputes between the parties are not resolved after following the applicable dispute resolution procedures or if either party determines to discontinue clinical development for medical, scientific, legal or other reasons.

The Pfizer Agreement does not grant any right of first negotiation to participate in future clinical studies, and each of the parties retains all rights and ability to evaluate their respective compounds.

License Agreement with Aurigene

In June 2022, we entered into an exclusive global license agreement with Aurigene Discovery Technologies Limited, or Aurigene, to research, develop and commercialize novel small molecule inhibitors of an undisclosed oncology target, or the Aurigene Agreement.

Under the terms of the Aurigene Agreement, Aurigene will provide to us an exclusive license to its portfolio of novel small molecule inhibitors of the target. Financial terms of the Aurigene Agreement include a \$8.0 million upfront payment from us for rights to a pre-existing Aurigene program and potential future milestone payments of up to \$60.0 million in clinical development and regulatory milestones, and up to \$370.0 million in commercial milestones. Aurigene is also eligible to receive mid-single-digit to low double-digit royalties on product sales, if any. During the research term, we will contribute funding to Aurigene to facilitate Aurigene's ongoing discovery efforts. We and Aurigene will jointly direct further preclinical work and, if successful, we will lead clinical development as well as regulatory and commercial activities. We and Aurigene jointly own collaboration compounds and rights to any inventions made during the research term.

The term of the Aurigene Agreement will continue until the expiration of the last-to-expire of all payment obligations with respect to all licensed products thereunder, unless terminated earlier in accordance with the terms of the Aurigene Agreement. The Aurigene Agreement may be terminated (a) by us for convenience, in our sole discretion, upon prior written notice to Aurigene, (b) by either us or Aurigene in connection with the other party's uncured material breach or (c) by either us or Aurigene in connection with the insolvency of the other party.

Intellectual Property

Our success depends, in part, on our ability to obtain, maintain and protect our intellectual property and other proprietary rights for OP-1250 and any future product candidates and other discoveries, inventions, trade secrets and know-how that are critical to our business operations. Our success also depends in part on our ability to operate without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of others, and in part, on our ability to prevent others from infringing, misappropriating or otherwise violating our intellectual property and proprietary rights. A comprehensive discussion on risks relating to intellectual property is provided under the section titled "Risk Factors—Risks Related to Our Intellectual Property."

Intellectual property rights relevant to pharmaceutical companies typically include a combination of patent rights, regulatory exclusivities, trademark rights, and trade secret protection. Our success depends, in part, on our ability to secure and enforce each of these types of intellectual property rights.

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. No consistent policy regarding the scope of claims allowable in patents in the field of biotechnology has emerged in the United States and in Europe, among other countries. Changes in the patent laws and rules, either by legislation, judicial decisions, or regulatory interpretation in other countries may diminish our ability to protect our inventions and enforce our intellectual property rights, and more generally could affect the value of our intellectual property. In particular, our ability to stop third parties from making, using, selling, offering to sell, importing or otherwise commercializing any of our patented inventions, either directly or indirectly, will depend

in part on our success in obtaining, defending and enforcing patent claims that cover our technology, inventions, and improvements. Regardless of the coverage we seek under our existing patent applications, there is always a risk that an alteration to the product or process may provide sufficient basis for a competitor to avoid infringement claims. In addition, the coverage claimed in a patent application can be significantly reduced before a patent is issued and courts can reinterpret patent scope after issuance. Moreover, many jurisdictions, including the United States, permit third parties to challenge issued patents in administrative proceedings, which may result in further narrowing or even cancellation of patent claims.

An issued patent provides its owner (or possibly its licensee) with a right to exclude others from making, using or selling that which is claimed in the patent, for a specified period of time (the “term” of the patent), in the jurisdiction in which the patent is issued. In the United States, and in many other countries, utility patents have a presumptive term of 20 years from their effective filing date (which is the earliest non-provisional filing date to which the patent claims priority). However, many jurisdictions, including the United States, require the payment of periodic annuities or maintenance fees for patents to remain in force for the full 20-year term. The United States also has provisions that require a patent term to be shortened if its claims are too similar to another patent owned by the same party that has a shorter term. The term of a patent, and the protection it affords, is therefore limited and once the patent term of our issued patents has expired, we may face competition. Because of the extensive time required for clinical development and regulatory review of the drugs we develop, it is possible that, before OP-1250 or any future product candidates we may develop can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of any such patent.

The United States and certain other jurisdictions also have provisions that permit extension of patent term for patents that claim a drug or drug product, or its approved use, if the patent was issued before clinical trials and were completed and regulatory approval secured, so long as certain specific requirements were satisfied. In the United States, such extension associated with regulatory approval is called a Patent Term Extension, or PTE, and it is limited to a maximum of five years, or less if the extended patent term would exceed 14 years after the date of regulatory approval. Only one patent can receive regulatory extension (e.g., PTE) per product approval.

The United States also offers a different form of patent term extension, known as Patent Term Adjustment, or PTA, whereby a particular patent’s term is automatically extended beyond the 20-year date if the United States Patent and Trademark Office, or the USPTO, caused delay during its examination; however, potentially available PTA is reduced by any amount of any delay caused by the patent applicant. We may not receive an extension if we fail to exercise due diligence during the testing phase or regulatory review process, fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. There can be no assurance that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

A provisional patent application can establish a priority date for a patent, but only if certain deadlines and procedures are met. Specifically, a non-provisional application must be filed within 12 months of the provisional filing date, and such non-provisional filing must be made by an applicant who has properly documented its right to claim priority. Furthermore, if any changes are made to the application between the provisional and the non-provisional filings, the changed material may not be entitled to the priority filing date. Still further, in the biopharmaceutical industry, it is common for applicants to file a so-called “international” patent application under the Patent Cooperation Treaty, or PCT, as a non-provisional filing. Such an international application, often referred to as a “PCT application,” like a provisional application, cannot itself issue as a patent but rather preserves the applicant’s right to pursue patent filings in individual countries, which patent filings are referred to as “national applications” or “national phase filings” and can claim the benefit of priority to the prior PCT application (which may in turn claim priority to the prior provisional filing). For most jurisdictions, national phase applications claiming priority to a PCT application must be filed within 30 to 32 months of the PCT’s earliest priority date. If we fail to meet the deadline for filing non-provisional or national phase applications, or fail to complete all procedural requirements associated with such filings, we may lose our right to claim priority.

Moreover, even if we comply with all deadlines and requirements, we may not be able to issue patents in relevant jurisdictions, and furthermore cannot predict whether any patents that might issue will provide us with any competitive advantage.

We have granted patents and pending applications relating to OP-1250, including granted claims that encompass the OP-1250 compound, pharmaceutical compositions that include OP-1250, and certain methods of using OP-1250, including in treatment which may involve combination therapy. The 20-year term for these patents expires in 2036. In the United States, it is uncertain whether any PTE will be available, and if so, how much. Additional applications are pending, including ones that relate to dosing regimens and treatment of particular cancers and patient populations, and, if granted, will have 20-year terms that expire between 2040 and 2043.

Certain patents related to OP-1250 may be eligible for PTE in certain jurisdictions, including the United States and Europe, upon approval of a commercial use of the corresponding product by a regulatory agency in the jurisdiction where the patent was granted. However, there can be no assurance that we will receive or benefit from any PTE with respect to such patents.

In addition to patent term extension regulatory exclusivities, pharmaceutical marketing approval agencies, such as the FDA and the EMA, offer certain data exclusivities for first-approved products with a new chemical entity, or NCE, exclusivity, and/or for approvals related to orphan indications, or Orphan Drug designation, and/or pediatric approvals, or Pediatric Exclusivity.

Furthermore, as OP-1250 has not previously been approved in the United States for any indication, OP-1250 may be eligible for five years of NCE exclusivity upon its first approval. Should that approval be for an orphan indication for which we have received Orphan Drug designation, the NCE and Orphan Drug exclusivity would run concurrently.

With respect to our owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any current patents or any patents that may be granted to us in the future will be commercially useful in protecting OP-1250 or any future product candidates and the methods used to manufacture them. Moreover, any issued patents and those that may issue in the future may not guarantee us the right to practice our technology in relation to the commercialization of OP-1250 or any future product candidates. Any patents and those that may issue in the future may be challenged, narrowed, circumvented or invalidated, which could limit our ability to stop competitors from marketing related product candidates or limit the length of the term of patent protection that we may have for OP-1250 or any future product candidates. In addition, the rights granted under any issued patents may not provide us with complete protection or competitive advantages against competitors with similar products to ours. For information regarding risks related to intellectual property, see the section titled “Risk Factors—Risks Related to Our Intellectual Property.”

We have also applied to register the “Olema,” “Olema Oncology,” “Olema Oncology and design,” and “Olema Therapeutics” trademarks with the USPTO. We do not currently own any U.S. registered trademarks for our brand or trade names. Our trademarks or trade names may be challenged, infringed, circumvented, or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively, and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

In addition to patent, regulatory exclusivity, and trademark, we rely on trade secret and know-how protection to secure our proprietary position around our chemistry, technology and other discoveries and inventions that we consider important to our business.

We also seek to protect our intellectual property, including our trade secrets and know-how, in part by entering into confidentiality agreements with companies with whom we share proprietary and confidential information in the course of business discussions, and by having confidentiality terms in our agreements with our employees, consultants, scientific advisors, clinical investigators and other contractors and also by requiring our employees, commercial contractors, and certain consultants and investigators, to enter into invention assignment agreements that grant us ownership of any discoveries or inventions made by them while in our employ. However, trade secrets and know-how can be difficult to protect. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes or that these agreements will afford us adequate protection of our intellectual property and proprietary rights. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. For information regarding risks related to intellectual property, see the section titled “Risk Factors—Risks Related to Our Intellectual Property.”

Sales and Marketing

Given our stage of development, we have not yet established a commercial organization or distribution capabilities. We intend to build a commercial infrastructure to support sales of any approved products. We intend to continue evaluating opportunities to work with partners that enhance our capabilities with respect to the development and commercialization of OP-1250. In addition, we intend to commercialize our product candidates, if approved, in key markets either alone or with partners in order to maximize the worldwide commercial potential of our programs.

Manufacturing

We currently do not own or operate any manufacturing facilities. We rely, and expect to continue to rely for the foreseeable future, on third-party contract manufacturing organizations, or CMOs, to produce OP-1250 for nonclinical and clinical testing, as well as for commercial manufacture if OP-1250 receives marketing approval. We require that our CMOs produce bulk drug substances and finished drug products in accordance with current Good Manufacturing Practices, or cGMPs, and all other applicable laws and regulations. We maintain agreements with our manufacturers that include confidentiality and intellectual property provisions to protect our proprietary rights related to OP-1250.

We have engaged CMOs to manufacture and package OP-1250 for nonclinical and clinical use. Additional CMOs are used to label and distribute OP-1250 for clinical use. We obtain our supplies from these CMOs on a purchase order basis and do not have long-term supply arrangements in place. Although we do not currently have contractual arrangements in place for redundant supply for OP-1250, it is our goal to identify and contract with at least two manufacturers for active pharmaceutical ingredient and two manufacturers for drug product. More broadly, for OP-1250 and any other product candidates we may develop, we intend to identify and qualify additional manufacturers to provide the active pharmaceutical ingredient and fill-and-finish services prior to seeking regulatory approval.

Competition

The biotechnology and pharmaceutical industries are characterized by rapid technological advancement, significant competition and an emphasis on intellectual property. We face potential competition from many different sources, including major and specialty pharmaceutical and biotechnology companies, academic research institutions, governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with current therapies and new therapies that may become available in the future.

Many of the companies against which we may compete have significantly greater financial resources and expertise in research and development, manufacturing, nonclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and oncology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or less expensive than any products we may develop. Our competitors also may obtain FDA or other regulatory approval for their product candidates more rapidly than we may obtain approval for ours, which could result in competitors establishing a strong market position before we are able to enter the market. We believe that the key competitive factors affecting the success of any of our product candidates, if approved, will include efficacy, combinability, safety profile, convenience, cost, level of promotional activity devoted to them and intellectual property protection.

If the product candidates for our priority programs are approved for the indications we are currently targeting, they will compete with the products discussed below. Furthermore, it is possible that other companies are also engaged in discovery or nonclinical development of product candidates for the same indications. These competitors, if successful in clinical development, may achieve regulatory approval and market adoption in advance of our product candidates, constraining our ability to gain significant market share for such product candidates. In addition, our product candidates, if approved, will compete with multiple approved products or products that may be approved for future indications for which we develop such product candidate.

There are several currently marketed drugs and product candidates currently in development for the treatment of ER+ breast cancer that target the estrogen receptor that may compete with OP-1250: including fulvestrant, marketed as Faslodex® by AstraZeneca PLC and or any generic equivalents of Faslodex® that are marketed or in development; elacestrant, marketed as ORSERDU™ by Stemline Therapeutics Inc.; giredestrant (GDC-9545), being developed by Roche Holding AG/Genentech, Inc.; camizestrant (AZD9833), being developed by AstraZeneca PLC; imlunestrant (LY3484356), being developed by Eli Lilly and Co.; ARV-471, being developed by Arvinas, Inc.; and lasofoxifene, being developed by Sermonix Pharmaceuticals.

Government Regulation and Product Approval

As a biopharmaceutical company that operates in the United States, we are subject to extensive regulation. Government authorities in the United States (at the federal, state and local level) and in other countries extensively regulate, among other things, the research, development, testing, manufacturing, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products such as those we are developing. Any drug candidates that we develop must be approved by the FDA before they may be legally marketed in the United States and by the appropriate foreign regulatory agency before they may be legally marketed in foreign countries. Generally, our activities in other countries will be subject to regulation that is similar in nature and scope as that imposed in the United States, although there can be important differences. Additionally, some significant aspects of regulation in Europe are addressed in a centralized way, but country-specific regulation remains essential in many respects.

U.S. Drug development process

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act, or FDCA, and implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. FDA sanctions could include, among other actions, refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of extensive nonclinical laboratory tests, nonclinical animal studies and formulation studies in accordance with applicable regulations, including the FDA's Good Laboratory Practices, or GLP, regulations and other applicable regulations;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with applicable regulations, including the FDA's current good clinical practice, or GCP, regulations to establish the safety and efficacy of the proposed drug for its proposed indication;
- submission to the FDA of a New Drug Application, or NDA, for a new drug;

- a determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with the FDA's current good manufacturing practice, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- potential FDA audit of the nonclinical and/or clinical trial sites that generated the data in support of the NDA;
- satisfactory completion of an FDA advisory committee review, if applicable; and
- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States.

Before testing any compounds with potential therapeutic value in humans, the drug candidate enters the nonclinical testing stage. Nonclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies, to assess the characteristics and potential safety and activity of the drug candidate. The conduct of the nonclinical tests must comply with federal regulations and requirements including GLPs. The sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. Some nonclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance.

For each successive clinical trial conducted with the investigational drug, a separate, new protocol submission to an existing IND must be made, along with any subsequent changes to the investigational plan. Sponsors are also subject to ongoing reporting requirements, including submission of IND safety reports for any serious adverse experiences associated with use of the investigational drug or findings from nonclinical studies suggesting a significant risk for human subjects, as well as IND annual reports on the progress of the investigations conducted under the IND.

Clinical trials involve the administration of the drug candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- Phase 1. The drug is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion, the side effects associated with increasing doses and if possible, to gain early evidence of effectiveness. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- Phase 2. The drug is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases or conditions and to determine dosage tolerance, optimal dosage and dosing schedule.
- Phase 3. Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall benefit/risk ratio of the product and provide an adequate basis for product approval. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of an NDA.

Post-approval studies, or Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 trials. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events or any finding from tests in laboratory animals that suggests a significant risk for human subjects.

Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA, the IRB, or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk.

Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final drug. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

U.S. review and approval processes

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product. Data may come from company-sponsored clinical trials intended to test the safety and effectiveness

of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug product to the satisfaction of the FDA. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances.

In addition, the Pediatric Research Equity Act, or PREA, requires a sponsor to conduct pediatric clinical trials for most drugs, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, original NDAs and supplements must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must evaluate the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor or FDA may request a deferral of pediatric clinical trials for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug is ready for approval for use in adults before pediatric clinical trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric clinical trials begin. The FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation. Unless otherwise required by regulation, the Pediatric Research Equity Act does not apply to any drug for an indication for which orphan designation has been granted. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has a goal of ten months from the date of “filing” of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to the FDA because the FDA has approximately two months to make a “filing” decision after it the application is submitted. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use and whether the product is being manufactured in accordance with cGMP to assure and preserve the product’s identity, strength, quality and purity. The FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions and typically follows the advisory committee’s recommendations.

Before approving an NDA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA may inspect one or more clinical sites to assure compliance with GCP requirements. After the FDA evaluates the application, manufacturing process and manufacturing facilities, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application will not be approved in its present form. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or (an) additional pivotal Phase 3 clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a Complete Response Letter is

issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical trials. For example, the FDA may require Phase 4 testing, which involves clinical trials designed to further assess a drug safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA may also determine that a risk evaluation and mitigation strategy, or REMS, is necessary to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS; the FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools.

Expedited development and review programs

The FDA has a fast track designation program that is intended to expedite or facilitate the process for reviewing new drug products that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Unique to a fast track product, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

Any product submitted to the FDA for approval, including a product with a fast track designation, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. A product is eligible for priority review if it has the potential to provide safe and effective therapy for a serious condition where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a serious condition compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for priority review in an effort to facilitate the review.

In addition, a product may be eligible for accelerated approval. Drug products intended to treat serious or life-threatening diseases or conditions may be eligible for accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires, as a condition for accelerated approval, pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast track designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. In addition, this designation may not provide a material commercial advantage.

Post-approval requirements

Any drug products for which we receive FDA approvals are subject to continuing regulation by the FDA, including, among other things, record-keeping requirements, reporting of adverse experiences with the product, providing the FDA with updated safety and efficacy information, product sampling and distribution requirements, and complying with FDA promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, restrictions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), limitations on industry-sponsored scientific and educational activities, and requirements for promotional activities involving the internet. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses.

In addition, quality control and manufacturing procedures must continue to conform to applicable manufacturing requirements after approval to ensure the long-term stability of the drug product. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including, among other things, recall or withdrawal of the product from the market. In addition, changes to the manufacturing process are strictly regulated, and depending on the significance of the change, may require prior FDA approval before being implemented. Other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

The FDA also may require post-marketing testing, known as Phase 4 testing, and surveillance to monitor the effects of an approved product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

U.S. Patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents, if granted, may be eligible for limited PTE under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. As compensation for patent term lost during product development and the FDA regulatory review process, the Hatch-Waxman Amendments permit a patent restoration term, or PTE, which is limited to a maximum of five years, or less if the extended patent term would exceed 14 years after the date of the regulatory approval of the product. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug or drug product, or its approved use, is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of a patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration

date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA. However, we may not receive an extension if we fail to exercise due diligence during the testing phase or regulatory review process, fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. There can be no assurance that we will benefit from any PTE or favorable adjustment to the term of any of our patents.

Market exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not approve or even accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovative drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA alternatively provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of non-patent market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued "Written Request" for such a trial.

Other U.S. Healthcare laws and compliance requirements

Although we currently do not have any products on the market, we are and, upon approval and commercialization, will be subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which we conduct our business. In the United States, such laws include, without limitation, state and federal fraud and abuse (such as anti-kickback and false claims), privacy and security, price reporting, and provider transparency laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term remuneration has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. The exceptions and safe harbors are drawn narrowly and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor but the exceptions and safe harbors are drawn narrowly and require strict compliance in order to offer protection.

Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Our practices may not in all cases meet all of the criteria for protection under a statutory exception or regulatory safe harbor.

Additionally, the intent standard under the Anti-Kickback Statute and certain criminal healthcare fraud statutes (discussed below) was amended by the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, together with subsequent amendments and regulations, collectively, the ACA, to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act (discussed below).

The federal False Claims Act prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to, or approval by, the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes “any request or demand” for money or property presented to the U.S. government. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product and for causing false claims to be submitted because of the companies’ marketing of the product for unapproved, and thus non- covered, uses.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created new federal criminal statutes that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Additionally, the federal Physician Payments Sunshine Act within the ACA, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program (with certain exceptions) annually report information related to certain payments or other transfers of value made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, certain ownership and investment interests held by these physicians and their immediate family members.

We may also be subject to data privacy and security regulations promulgated by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, impose requirements on covered entities, including certain healthcare providers, health plans, and healthcare clearinghouses, and their respective business associates that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity as well as their covered subcontractors relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA’s privacy and security standards directly applicable to business associates, independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys

general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of pharmaceutical products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, track and report gifts, compensation and other remuneration made to physicians and other healthcare providers, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

If our operations are found to be in violation of any of the federal and state healthcare laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including without limitation, civil, criminal and/or administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government programs, such as Medicare and Medicaid, injunctions, private "quitam" actions brought by individual whistleblowers in the name of the government, or refusal to allow us to enter into government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

U.S. and foreign laws, regulations, rules, contractual obligations, policies and other obligations related to data privacy and security.

We are or will become subject to privacy laws in the jurisdictions in which we are established or in which we sell or market our products or run clinical trials. For example, in Europe we are subject to the General Data Protection Regulation, or GDPR, in relation to our collection, control, processing and other use of personal data (i.e., data relating to an identified or identifiable living individual). We process personal data in relation to participants in our clinical trials in the European Economic Area, or EEA, including the health and medical information of these participants. The GDPR is directly applicable in each European Union Member State, however, it provides that European Union Member States may introduce further conditions that could cause our compliance costs to increase, ultimately having an adverse impact on our business.

We are subject to the supervision of local data protection authorities in those European Union jurisdictions where we are established or otherwise subject to the GDPR. Fines for certain breaches of the GDPR are significant: up to the greater of €20 million or 4% of total global annual turnover. Further, we must comply with both the GDPR and separately the GDPR as implemented in the United Kingdom, or UK, each regime having the ability to fine up to the greater of €20 million / £17 million or 4% of global turnover. A breach of the GDPR or other applicable privacy and data protection laws and regulations could result in regulatory investigations, reputational damage, orders to cease/change our use of data, enforcement notices, or potential civil claims including class action type litigation. In general, if our efforts to comply with the GDPR or other applicable European Union laws and regulations are not successful, it could adversely affect our business in the European Union.

In the ordinary course of business, we may transfer personal data from Europe and other jurisdictions to the United States or other countries. Europe and other jurisdictions have enacted laws requiring data to be localized or limiting the transfer of personal data to other countries. In particular, the EEA and the UK have significantly

restricted the transfer of personal data to the United States and other countries whose privacy laws it believes are inadequate. Other jurisdictions may adopt similarly stringent interpretations of their data localization and cross-border data transfer laws. Although there are currently various mechanisms that may be used to transfer personal data from the EEA and UK to the United States in compliance with law, such as the EEA and UK's standard contractual clauses, these mechanisms are subject to legal challenges, and there is no assurance that we can satisfy or rely on these measures to lawfully transfer personal data to the United States.

If there is no lawful manner for us to transfer personal data from the EEA, the UK or other jurisdictions to the United States, or if the requirements for a legally-compliant transfer are too onerous, we could face significant adverse consequences, including the interruption or degradation of our operations, the need to relocate part of or all of our business or data processing activities to other jurisdictions at significant expense, increased exposure to regulatory actions, substantial fines and penalties, the inability to transfer data and work with partners, vendors and other third parties, and injunctions against our processing or transferring of personal data necessary to operate our business. Additionally, companies that transfer personal data out of the EEA and UK to other jurisdictions, particularly to the United States, are subject to increased scrutiny from regulators, individual litigants, and activist groups. Some European regulators have ordered certain companies to suspend or permanently cease certain transfers out of Europe for allegedly violating the GDPR's cross-border data transfer limitations.

In the United States, the California Consumer Privacy Act, or CCPA, creates individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling certain personal data of consumers or households. The CCPA requires covered companies to provide new disclosure to consumers about such companies' data collection, use and sharing practices, provide such consumers new ways to opt-out of certain sales or transfers of personal information, and provide consumers with additional causes of action. The CCPA provides for civil penalties for violations, as well as a private right of action for certain data breaches that result in the loss of personal information. This private right of action may increase the likelihood of, and risks associated with, data breach litigation. The CCPA (a) allows enforcement by the California Attorney General, with fines set at \$2,500 per violation (i.e., per person) or \$7,500 per intentional violation and (b) authorizes private lawsuits to recover statutory damages for certain data breaches.

In addition, laws in all 50 U.S. states require businesses to provide notice to consumers whose personal information has been disclosed as a result of a data breach. State laws are changing rapidly and there is discussion in the U.S. Congress of a new comprehensive federal data privacy law to which we would become subject if it is enacted. The CCPA may impact our business activities and exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information. Additionally, the California Privacy Rights Act, or CPRA, significantly modifies the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. New legislation proposed or enacted in various other states will continue to shape the data privacy environment nationally. For example, Virginia, Colorado, Utah, and Connecticut have all enacted broad privacy legislation. Certain state laws may be more stringent or broader in scope, or offer greater individual rights, with respect to confidential, sensitive and personal information than federal, international or other state laws, and such laws may differ from each other, which may complicate compliance efforts. In addition to the foregoing, any breach of privacy laws or data security laws, particularly resulting in a significant security incident or breach involving the misappropriation, loss or other unauthorized use or disclosure of sensitive or confidential patient or consumer information, could have a material adverse effect on our business, reputation and financial condition. As a data controller, we will be accountable for any third-party service providers we engage to process personal data on our behalf, including our CROs. We attempt to mitigate the associated risks but there is no assurance that privacy and security-related safeguards will protect us from all risks associated with the third-party processing, storage and transmission of such information.

Pharmaceutical coverage, pricing and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we or our collaborators obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we or our collaborators receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage, and establish adequate reimbursement levels for such drug products. In the United States, third-party payors include federal and state healthcare programs, government authorities, private managed care providers, private health insurers and other organizations.

Third-party payors are increasingly challenging the price, examining the medical necessity and reviewing the cost-effectiveness of medical drug products and medical services, in addition to questioning their safety and efficacy. Such payors may limit coverage to specific drug products on an approved list, also known as a formulary, which might not include all of the FDA-approved drugs for a particular indication. We or our collaborators may need to conduct expensive pharmaco-economic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Nonetheless, our product candidates may not be considered medically necessary or cost-effective. Moreover, the process for determining whether a third-party payor will provide coverage for a drug product may be separate from the process for setting the price of a drug product or for establishing the reimbursement rate that such a payor will pay for the drug product. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

If we elect to participate in certain governmental programs, we may be required to participate in discount and rebate programs, which may result in prices for our future products that will likely be lower than the prices we might otherwise obtain. For example, drug manufacturers participating under the Medicaid Drug Rebate Program must pay rebates on prescription drugs to state Medicaid programs. Under the Veterans Health Care Act, or VHCA, drug companies are required to offer certain drugs at a reduced price to a number of federal agencies, including the U.S. Department of Veterans Affairs and Department of Defense, the Public Health Service and certain private Public Health Service designated entities in order to participate in other federal funding programs, including Medicare and Medicaid. Recent legislative changes require that discounted prices be offered for certain U.S. Department of Defense purchases for its TRICARE program via a rebate system. Participation under the VHCA also requires submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations. If our products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply.

Different pricing and reimbursement schemes exist in other countries. In the European Union, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular drug candidate to currently available therapies. Across the European Union, member states carry out assessments of new pharmaceutical products from an economic, public health, and therapeutic perspective, through a Health Technology Assessment, or HTA, process, which is currently governed by the national laws of member states. In December 2021, the European Parliament voted to implement a regulation regarding HTAs, or the HTA Regulation. The HTA Regulation is scheduled to apply as of January 2025, and will provide a framework for pan-EU clinical assessments, scientific consultations, identification of emerging health technologies, and further cooperation. Entry into application of the Regulation could impose stricter and more detailed procedures to be followed by marketing authorization holders concerning conduct of HTAs in relation to their products which may influence related pricing and reimbursement decisions. However, under the HTA Regulation, member states

will still be free to make their own pricing and reimbursement decisions. Moreover, member states may, and do, choose to restrict the range of products for which their national health insurance systems or national healthcare systems provide reimbursement and to control the prices of such products. Member states may impose direct controls on pricing, or otherwise adopt a system of direct or indirect controls on the profitability of the companies placing such products on the market. Other member states allow companies to set their own prices but monitor and control prescription volumes and issue guidance to medical professionals to limit prescriptions of such products. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any product candidates for which we or our collaborators receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we or our collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Healthcare reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products and services, implementing reductions in Medicare and other healthcare funding and applying new payment methodologies. For example, in March 2010, the ACA was enacted, which affected existing government healthcare programs and resulted in the development of new programs.

There have been executive, judicial and Congressional challenges to certain aspects of the ACA. For example, on June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the “individual mandate” was repealed by Congress. In addition, there have been a number of health reform initiatives by the Biden administration that have impacted the ACA. For example, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or the IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. The IRA also eliminates the “donut hole” under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and creating a new manufacturer discount program. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how such challenges and the healthcare reform measures of the Biden administration will impact the ACA and our business.

Other legislative changes have also been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013, and will remain in effect through 2031. Under current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug’s average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024.

There has been heightened governmental scrutiny recently over the manner in which pharmaceutical companies set prices for their marketed products, which has resulted in several Presidential executive orders, Congressional inquiries and proposed federal legislation, as well as state efforts, designed to, among other

things, bring more transparency to product pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At the federal level, in July 2021, the Biden administration released an executive order that included multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, the U.S. Department of Health and Human Services, or HHS, released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform. The plan sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. In addition, the IRA, among other things (i) directs HHS to negotiate the price of certain high-expenditure, single-source drugs and biologics covered under Medicare and (ii) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions will take effect progressively starting in fiscal year 2023, although they may be subject to legal challenges. In addition, the Biden administration released an additional executive order on October 14, 2022, directing HHS to report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

In addition, it is possible that there will be further legislation or regulation that could harm our business, financial condition, and results of operations.

The U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act of 1977, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Europe / rest of world government regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. Whether or not we or our potential collaborators obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries.

Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, pursuant to the Clinical Trials Regulation, which came into application on January 31, 2022, a clinical trial application, or CTA, must be submitted to via the EMA's Clinical Trials Information System, which will cover all regulatory and ethics assessments from the member states concerned. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed. Approval and monitoring of clinical trials in the European Union is the responsibility of individual member states but, compared to the position prior to the applicability of the Clinical Trials Regulation, there is likely to be more collaboration, information-sharing, and decision-making between member states.

The requirements and processes governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all major territories, including the European Union, clinical trials

must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The European Union and the European Economic Area consist, at the time of writing, of the twenty-seven Member States of the European Union, plus Norway, Iceland and Liechtenstein which are Member States of the European Economic Area. To obtain regulatory approval of an investigational drug or biological product under European Union regulatory systems, we must submit a marketing authorization application either under the so-called centralized or national authorization procedures. There are three procedures for a marketing authorization to be obtained:

- The Centralized marketing authorization, which is issued by the European Commission through the Centralized Procedure, based on the scientific opinion of the EMA's Committee for Medicinal Products for Human Use, and which is valid throughout the entire territory of the European Economic Area. The Centralized Procedure is mandatory for certain types of products, such as (i) biotechnology medicinal products such as genetic engineering, (ii) orphan medicinal products, (iii) medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases and (iv) advanced-therapy medicines, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the European Union, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the European Union.
- Decentralized Procedure marketing authorizations are available for products not falling within the mandatory scope of the Centralized Procedure. An identical dossier is submitted to the competent authorities of each of the Member States in which the marketing authorization is sought, one of which is selected by the applicant as the Reference Member State, or RMS, to lead the evaluation of the regulatory submission. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet as distilled from the preliminary evaluation, which are sent to the other Member States (referred to as the Concerned Member States) for their approval. If the Concerned Member States raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the RMS records the agreement, closes the procedure and informs the applicant accordingly. Each Member State concerned by the procedure is required to adopt a national decision to grant a national marketing authorization in conformity with the approved assessment report, SmPC and the labeling and package leaflet as approved. Where a product has already been authorized for marketing in a Member State of the European Economic Area, the granted national marketing authorization can be used for mutual recognition in other Member States through the Mutual Recognition Procedure, or MRP, resulting in progressive national approval of the product in the European Economic Area.
- National marketing authorizations, which are issued by a single competent authority of the Member States of the European Economic Area and only covers such authority's respective territory, are also available for products not falling within the mandatory scope of the Centralized Procedure. Once a product has been authorized for marketing in a Member State of the European Economic Area through the National Procedure, this National marketing authorization can also be recognized in other Member States through the Mutual Recognition Procedure.

The EMA grants orphan drug designation to promote the development of products that may offer therapeutic benefits for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the European Union. In addition, orphan drug designation can be granted if the drug is intended for a life threatening, seriously debilitating or serious and chronic condition in the European Union and without incentives it is unlikely that sales of the drug in the European Union would be sufficient to justify developing the drug. Orphan drug designation is only available if there is no other satisfactory method approved in the European Union of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients. Orphan drug designation provides opportunities for free protocol assistance, fee reductions for access to the centralized regulatory procedures and ten years of market

exclusivity following drug approval, which can be extended to 12 years if trials are conducted in accordance with an agreed-upon pediatric investigational plan. The exclusivity period may be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all major territories, clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. If we or our potential collaborators fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Employees and Human Capital

As of January 31, 2023, we had 86 employees, 83 of whom were full time, consisting of clinical, research, operations, regulatory, finance and business development personnel. Thirty-two of our employees hold Ph.D. or M.D. degrees. None of our employees is subject to a collective bargaining agreement. We consider our relationship with our employees to be good.

Our commitment to innovation begins with the commitment to creating an environment with the ability to attract and retain highly skilled people, including top scientific talent, as a critical factor for us to deliver on our mission and create value.

As we have grown significantly since our initial public offering in November 2020, we have focused on diversity, inclusion and belonging both at the Board level, where we appointed three global biotech female leaders to our Board, and for all employees. We have been successful in hiring employees with a broad diversity of experiences and backgrounds. We face significant competition for biotechnology talent from both established and early-stage biotechnology companies. Further, we are headquartered in the San Francisco Bay Area and have operations in Cambridge, Massachusetts, both global biotechnology hubs with many employment choices. Despite our early stage, we have been successful in hiring highly qualified staff to join Olema. As of January 31, 2023, 54% of our employee population is male, and 46% is female.

We strive to create a positive employee experience by fostering an inclusive and equitable culture. We are committed to the health, safety, and well-being of our employees, with a particular focus on COVID-19 related protections and precautions for our workforce. This commitment is reflected in our ability to attract and retain high performers. We believe we have a robust employment package that promotes well-being across all aspects of our employees' lives, including healthcare, paid time-off, retirement savings with a company match through a 401(k) plan, our equity incentive plans, and our employee stock purchase plan. The principal purposes of our equity incentive plans are to attract, motivate and retain our employees and directors through the granting of stock-based compensation awards. From time to time, we may offer additional stock-based compensation awards to our employees to continue to motivate them and support retention, particularly at times when our stock price, or the stock price of biotechnology companies generally, is volatile. We grant stock options to all full-time employees to foster alignment and promote a spirit of ownership.

Corporate Information

We were incorporated in Delaware on August 7, 2006 under the legal name of CombiThera, Inc., and, on March 25, 2009, were renamed Olema Pharmaceuticals, Inc.

Available Information

Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Exchange Act, are filed with the SEC.

Such reports and other information filed by us with the SEC are available free of charge on the Investors section of our website, www.olema.com, when such reports are available on the SEC's website. The SEC maintains an internet site that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC at www.sec.gov. The information contained on the websites referenced in this Annual Report on Form 10-K is not incorporated by reference into this filing. Further, any references to website URLs are intended to be inactive textual references only.

Item 1A. Risk Factors.

Risks related to our financial position and the need for additional capital

We have not completed any clinical trials and have no products approved for commercial sale, which may make it difficult for you to evaluate our current business and predict our future success and viability.

We are a clinical-stage biopharmaceutical company, and we have no products approved for commercial sale, have not generated any revenue from product sales and have incurred losses since inception. To date, we have devoted substantially all of our resources and efforts to organizing and staffing our company, business planning, executing partnerships, raising capital, discovering, identifying and developing our product candidate, OP-1250, securing related intellectual property rights and conducting nonclinical studies and a Phase 1/2 clinical study of OP-1250. We have not yet demonstrated our ability to successfully complete any clinical trials, obtain marketing approvals, manufacture a commercial-scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. As a result, it may be more difficult for you to accurately predict our future success or viability than it could be if we had a longer operating history.

In addition, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and risks frequently experienced by clinical-stage biopharmaceutical companies in rapidly evolving fields. We also may need to transition from a company with a research focus to a company capable of successfully executing drug development activities and supporting commercial operations. If we do not adequately address these risks and difficulties or successfully make such a transition, our business, financial condition, results of operations and prospects will be significantly harmed.

We require substantial additional capital to finance our operations. If we are unable to raise such capital when needed, or on acceptable terms, we may be forced to delay, reduce and/or eliminate one or more of our research and drug development programs of our only product or future commercialization efforts.

Developing pharmaceutical products, including conducting nonclinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. Our operations have consumed substantial amounts of cash since inception, and we expect our expenses will increase in connection with our ongoing activities, particularly as we initiate and conduct clinical trials of, and seek marketing approval for, OP-1250. We anticipate incurring significant costs associated with the development of OP-1250 and any future drug candidates we may develop. Our expenses could increase beyond expectations if we are required by the FDA, the EMA, or other regulatory agencies to perform clinical trials or nonclinical studies in addition to those that we currently anticipate. Other unanticipated costs may also arise. In addition, if we obtain marketing approval for OP-1250, we expect to incur significant commercialization expenses related to drug sales, marketing, manufacturing and distribution. Because the design and outcome of our planned and anticipated clinical trials are highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of any product candidate we develop. We also incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in order to maintain our continuing operations.

As of December 31, 2022, we had \$204.4 million in cash, cash equivalents, and marketable securities. Based on our current operating plans, we believe that our cash, cash equivalents, and marketable securities as of December 31, 2022 will be sufficient to fund our operating expenses and capital expenditures requirements into 2025. Our estimate as to how long we expect our existing cash, cash equivalents and marketable securities to be able to continue to fund our operating expenses and capital expenditures requirements is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Changing circumstances, some of which may be beyond our control, including a default in one or several of the financial institutions in which we hold, or a negative return on, our cash and cash equivalents, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Moreover, it is particularly difficult to estimate with certainty our future expenses given the dynamic nature of our business and the geopolitical and macroeconomic environment, generally, including the COVID-19 pandemic and the ongoing conflict between Ukraine and Russia and related sanctions. Advancing the development of OP-1250 and any future product candidates we may develop will require a significant amount of capital, and our existing cash, cash equivalents and marketable securities will not be sufficient to fund all of the activities that are necessary to complete the development of OP-1250.

We will be required to obtain additional funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources, which may dilute our stockholders or restrict our operating activities. Adequate additional financing may not be available to us on acceptable terms, or at all. Market volatility, including as a result of geopolitical and macroeconomic events such as the COVID-19 pandemic and the ongoing conflict between Ukraine and Russia and related sanctions, could adversely increase our need to access capital and likewise, adversely impact our ability to access capital as and when needed. For example, inflation rates, particularly in the United States, have increased recently to levels not seen in years, and increased inflation may result in increases in our operating costs (including our labor costs), reduced liquidity and limits on our ability to access credit or otherwise raise capital on acceptable terms, if at all. In addition, the U.S. Federal Reserve has raised, and may again raise, interest rates in response to concerns about inflation, which, coupled with reduced government spending and volatility in financial markets may have the effect of heightening these risks and further increasing economic uncertainty. Our failure to raise capital as and when needed or on acceptable terms would have a negative impact on our financial condition and our ability to pursue our business strategy, and we may have to delay, reduce the scope of, suspend or eliminate one or more of our research-stage programs, clinical trials or future commercialization efforts. We also could be required to seek collaborators for OP-1250 or any future product candidate at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available or relinquish or license on unfavorable terms our rights to our product candidates in markets where we otherwise would seek to pursue development or commercialization ourselves. Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

We have incurred net losses since inception, and we expect to continue to incur net losses for the foreseeable future. In addition, we may be unable to continue as a going concern over the long term.

We have incurred net losses in each reporting period since our inception, have not generated any revenue from product sales to date and have financed our operations principally through our initial public offering and private financings. We have incurred net losses of \$104.8 million and \$71.1 million for the years ended December 31, 2022 and 2021, respectively. We had an accumulated deficit of \$209.0 million as of December 31, 2022. Our losses have resulted principally from expenses incurred in research and development of OP-1250 and from management and administrative costs and other expenses that we have incurred while building our business infrastructure. Our only product candidate, OP-1250, is in early-stage clinical trials. As a result, we expect that it will be several years, if ever, before we have a commercialized product and generate revenue from product sales. Even if we succeed in receiving marketing approval for and commercializing OP-1250 in one of our lead indications, we expect that we will continue to incur substantial research and development and other expenses as we continue the clinical development programs for OP-1250 in other indications.

We expect to continue to incur increased expenses and operating losses for the foreseeable future as we continue our research and development efforts and seek to obtain regulatory approval for OP-1250. The net losses we incur may fluctuate significantly from quarter to quarter such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had, and will continue to have, an adverse effect on our working capital. In any particular period, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

In addition, our consolidated financial statements for the years ended December 31, 2022 and 2021 included elsewhere in this Annual Report have been prepared assuming we will continue as a going concern. However, we have incurred losses and negative cash flows from operations. As a development stage company, we expect to incur significant and increasing losses until regulatory approval is granted for OP-1250. Regulatory approval is not guaranteed and may never be obtained. As a result, these conditions raise substantial doubt about our ability to continue as a going concern over the long term.

We have never generated revenue from product sales and may never be profitable.

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with our collaboration partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, OP-1250 and any future product candidates we may develop. We do not anticipate generating revenue from product sales for the next several years, if ever. Our ability to generate revenue from product sales depends heavily on our and our current and potential future collaborators' success in:

- completing clinical and nonclinical development of our product candidate and programs and identifying and developing new product candidates;
- seeking and obtaining marketing approvals for any product candidates that we develop;
- launching and commercializing product candidates for which we obtain marketing approval by establishing a sales force, marketing, medical affairs and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- achieving adequate access and reimbursement by government and third-party payors for product candidates that we develop;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and the market demand for product candidates that we develop, if approved;
- obtaining market acceptance of product candidates that we develop as viable treatment options;
- addressing any competing technological and market developments;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations in such collaborations;
- maintaining, protecting, enforcing and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- defending against third-party interference, infringement or other intellectual property-related claims, if any; and

- attracting, hiring and retaining qualified personnel.

Even if OP-1250 or any future product candidate that we may develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA, the EMA or other comparable regulatory agencies to perform clinical trials or nonclinical studies in addition to those that we currently anticipate. Even if we are able to generate revenue from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

Risks related to the discovery, development and commercialization of our product candidate

We are substantially dependent on the success of our only product candidate, OP-1250, which is currently in the early stages of clinical development. If we are unable to complete development of, obtain regulatory approval for and commercialize OP-1250 in one or more indications and in a timely manner, our business, financial condition, results of operations and prospects will be significantly harmed.

Our future success is heavily dependent on our ability to timely complete clinical trials, obtain marketing approval for and successfully commercialize OP-1250, our only product candidate. We expect that a substantial portion of our efforts and expenses over the next several years will be devoted to the development of OP-1250 in our ongoing clinical trials in multiple indications. We are investing significant efforts and financial resources in the research and development of OP-1250. OP-1250 will require additional clinical development, evaluation of clinical, nonclinical and manufacturing activities, marketing approval from government regulators, and significant marketing efforts before we can generate any revenues from product sales. We are not permitted to market or promote OP-1250 before we receive marketing approval from the FDA and comparable foreign regulatory authorities, and we may never receive such marketing approvals. Should our planned clinical development of OP-1250 in our lead indications fail to be completed in a timely manner or at all, we will need to rely on our ongoing and planned clinical development of OP-1250 in additional indications, which will require more time and resources to obtain regulatory approval and proceed with commercialization and may ultimately be unsuccessful.

We cannot assure you that our planned clinical development programs for OP-1250 will be completed in a timely manner, or at all, or that we will be able to obtain approval for OP-1250 from the FDA, European Commission (based on the positive opinion of the EMA's Committee for Medicinal Products for Human Use, commonly referred to as EMA approval), or any comparable foreign regulatory authority. If we are unable to complete development of, obtain regulatory approval for and commercialize OP-1250 in one or more indications and in a timely manner, our business, financial condition, results of operations and prospects will be significantly harmed.

Clinical development is a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results. Failure can occur at any stage of clinical development. We have never completed a pivotal clinical trial or submitted a New Drug Application, or NDA, to the FDA or similar drug approval filings to comparable foreign authorities. If we are ultimately unable to obtain regulatory approval for OP-1250, we will be unable to generate product revenue and our business, financial condition, results of operations and prospects will be significantly harmed.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of nonclinical studies and early clinical trials of OP-1250 and any future product candidates we may develop may not be predictive of the results of subsequent clinical trials. We have a limited operating history and to date have not demonstrated our ability to complete large-scale clinical trials.

Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through nonclinical studies and initial clinical trials. In addition to the safety and efficacy traits of any product candidate, clinical trial failures may result from a multitude of factors including flaws in trial design, dose selection, placebo effect and patient enrollment criteria. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Based upon negative or inconclusive results, we or any potential future collaborator may decide, or regulators may require us, to conduct additional clinical trials or nonclinical studies. In addition, data obtained from trials and studies are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may delay, limit or prevent regulatory approval.

Our future clinical trials may not be successful. If any product candidate is found to be unsafe or lack efficacy, we will not be able to obtain regulatory approval for it and our business, financial condition, results of operations and prospects may be significantly harmed. In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in composition of the patient populations, adherence to the dosing regimen and other trial protocols and the dropout rate among clinical trial participants. Patients treated with OP-1250 or product candidates we may develop in the future may also be undergoing surgical, radiation and chemotherapy treatments and may be using other approved products or investigational new drugs, which can cause side effects or adverse events that are unrelated to OP-1250 or product candidates we may develop. As a result, assessments of efficacy can vary widely for a particular patient, and from patient to patient and site to site within a clinical trial. This subjectivity can increase the uncertainty of, and adversely impact, our clinical trial outcomes. We do not know whether any clinical trials we may conduct will demonstrate consistent or adequate efficacy and safety sufficient to obtain marketing approval to market OP-1250 or any future product candidates we may develop.

We do not know whether our current clinical trial of OP-1250 or any future clinical trials we may conduct will demonstrate consistent or adequate efficacy and safety to obtain regulatory approval to market OP-1250 or any future product candidates we may develop. Most product candidates that begin clinical trials are never approved by regulatory authorities for commercialization. If we are unable to bring OP-1250 or any future product candidates to market, our ability to create long-term stockholder value will be limited.

In addition, we may rely in part on nonclinical, clinical and quality data generated by CROs and other third parties for regulatory submissions for OP-1250. While we have or will have agreements governing these third parties' services, we have limited influence over their actual performance. If these third parties do not make data available to us, or, if applicable, make regulatory submissions in a timely manner, our development programs may be significantly delayed, and we may need to conduct additional studies or collect additional data independently. In either case, our development costs would increase.

Moreover, nonclinical and clinical data are often susceptible to varying interpretations and analyses and many companies that believed their product candidates performed satisfactorily in nonclinical studies and clinical trials nonetheless failed to obtain FDA, EMA or comparable foreign regulatory authority approval. We cannot guarantee that the FDA or foreign regulatory authorities will interpret trial results as we do, and more trials could be required before we are able to submit an application seeking approval of OP-1250 or any future product candidates we may develop. To the extent that the results of the trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of OP-1250 or any future product candidates we may develop. Even if regulatory approval is secured for OP-1250, the terms of such approval may limit the scope and use of OP-1250, which may also limit its commercial potential. Furthermore, the approval policies or regulations of the FDA, EMA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval, which may lead to the FDA, EMA or comparable foreign regulatory authorities delaying, limiting or denying approval of OP-1250, including and any other indication we are seeking for approval under OP-1250.

The regulatory approval processes of the FDA, EMA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for OP-1250 or any future product candidates we may develop, our business, financial condition, results of operations and prospects will be significantly harmed.

The time required to obtain approval by the FDA, EMA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions.

Applications for OP-1250 could fail to receive regulatory approval for many reasons, including the following:

- the FDA, EMA or other comparable foreign regulatory authorities may disagree with the design, implementation or results of our clinical trials;
- the FDA, EMA or other comparable foreign regulatory authorities may determine that OP-1250 is not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use;
- the population studied in the clinical trial may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- the FDA, EMA or other comparable foreign regulatory authorities may disagree with our interpretation of data from nonclinical studies or clinical trials;
- the data collected from clinical trials of OP-1250 may not be sufficient to support the submission of a NDA, or other submission or to obtain regulatory approval in the United States or elsewhere;
- we may be unable to demonstrate to the FDA, EMA or other comparable foreign regulatory authorities that OP-1250's risk-benefit ratio for its proposed indication is acceptable;
- the FDA, EMA or other comparable foreign regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA, EMA or other comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.
- This lengthy approval process, as well as the unpredictability of the results of clinical trials, may result in our failing to obtain regulatory approval to market OP-1250, which would significantly harm our business, financial condition, results of operations and prospects.

In addition, even if we obtain approval of OP-1250 for a lead indication, regulatory authorities may not approve OP-1250 for other indications, may impose significant limitations in the form of narrow indications, warnings, or a Risk Evaluation and Mitigation Strategy, or REMS. Certain regulatory authorities may grant approval contingent on the performance of costly post-marketing clinical trials or may approve OP-1250 with a label that does not include the labeling claims necessary or desirable for successful. In addition, regulatory authorities in certain countries may not approve the price we intend to charge for the product we develop. If we are unable to obtain regulatory approval of OP-1250, or if regulatory approval is limited, our business, financial condition, results of operation and prospects will be significantly harmed.

Delays in clinical trials are common and have many causes, and any delay could result in increased costs to us and jeopardize or delay our ability to obtain regulatory approval and commence product sales.

We may experience delays in clinical trials of OP-1250 or any future product candidate we may develop. Our planned clinical trials may not begin on time, have an effective design, enroll a sufficient number of patients, or be completed on schedule, if at all. Our clinical trials can be delayed for a variety of reasons, including delays related to:

- the FDA, EMA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical trials;
- obtaining regulatory authorizations to commence a trial or reaching a consensus with regulatory authorities on trial design;
- any failure or delay in reaching an agreement with CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining approval from one or more institutional review boards, or IRBs;
- IRBs refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional subjects, or withdrawing their approval of the trial;
- changes to clinical trial protocol;
- clinical sites deviating from trial protocol or dropping out of a trial;
- manufacturing sufficient quantities of product candidate or obtaining sufficient quantities of combination therapies for use in clinical trials;
- subjects failing to enroll or remain in our trial at the rate we expect, or failing to return for post-treatment follow-up;
- delays in enrollment by subjects, or completion of the trial by subjects, due to the COVID-19 pandemic;
- subjects choosing an alternative treatment for the indication for which we are developing OP-1250, or participating in competing clinical trials;
- lack of adequate funding to continue the clinical trial;
- subjects experiencing severe or unexpected drug-related adverse effects;
- regulatory authorities imposing a clinical hold;
- occurrence of serious adverse events in trials of the same class of agents conducted by other companies;
- selection of clinical end points that require prolonged periods of clinical observation or analysis of the resulting data;
- shutdowns, either temporarily or permanently, of any facility manufacturing OP-1250 or any future product candidate we may develop or any of their components, including by order from the FDA,

competent authorities of EU Member States or comparable foreign regulatory authorities due to violations of current good manufacturing practice, or cGMP, regulations or other applicable requirements, or infections or cross-contaminations of OP-1250 or any future product candidate we may develop in the manufacturing process;

- any changes to our manufacturing process that may be necessary or desired;
- third-party clinical investigators losing the licenses or permits necessary to perform our clinical trials, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, good clinical practices, or GCP, or other regulatory requirements;
- third-party contractors not performing data collection or analysis in a timely or accurate manner; or
- third-party contractors becoming debarred or suspended or otherwise penalized by the FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or all of the data produced by such contractors in support of our marketing applications.

In addition, disruptions caused by the COVID-19 pandemic may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials. For instance, as a result of industry-wide COVID-19 impacts on clinical sites, we have experienced subject enrollment timeline delays in a Phase 1b clinical study of OP-1250 in combination with another CDK4/6 inhibitor and with a PI3K α inhibitor.

We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, by a Data Safety Monitoring Board for such trial or by the FDA, competent authorities of EU Member States or comparable foreign regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA, competent authorities of EU Member States or comparable foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. In addition, changes in regulatory requirements and policies may occur, and we may need to amend clinical trial protocols to comply with these changes. Amendments may require us to resubmit our clinical trial protocols to IRBs for reexamination, which may impact the costs, timing or successful completion of a clinical trial.

Further, conducting clinical trials in foreign countries, as we may do for OP-1250 or product candidates we may develop in the future, presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries.

If we experience delays in the completion of, or termination of, any clinical trial of OP-1250 or any product candidates we may develop in the future, the commercial prospects of OP-1250 or any product candidates we may develop in the future will be harmed, and our ability to generate product revenues from OP-1250 or any product candidates we may develop in the future will be delayed. Moreover, any delays in completing our clinical trials will increase our costs, slow down OP-1250's or any product candidates we may develop in the future's development and approval process and jeopardize our ability to commence product sales and generate revenues.

In addition, many of the factors that cause, or lead to, termination or suspension of, or a delay in the commencement or completion of, clinical trials may also ultimately lead to the denial of regulatory approval of OP-1250 or any product candidates we may develop in the future. Any delays in our clinical trials that occur as

a result could shorten any period during which we may have the exclusive right to commercialize OP-1250 or any product candidates we may develop in the future and our competitors may be able to bring products to market before we do, and the commercial viability of OP-1250 or any product candidates we may develop in the future could be significantly reduced. Any of these occurrences may significantly harm our business, financial condition, results of operations and prospects.

Although we have received Fast Track designation for OP-1250 for ER+/HER2- metastatic breast cancer that has progressed following one or more lines of endocrine therapy with at least one line given in combination with a CDK4/6 inhibitor, we may be unable to obtain or maintain the benefits associated with such designation.

In July 2022, we were granted FDA Fast Track designation for OP-1250 for ER+/HER2- metastatic breast cancer that has progressed following one or more lines of endocrine therapy with at least one line given in combination with a CDK4/6 inhibitor. If a drug is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet medical needs for this condition, the sponsor may apply for FDA Fast Track designation for a particular indication. NDAs submitted for Fast Track designated drugs may qualify for priority review, accelerated approval and rolling submission under the policies and procedures offered by the FDA, but the Fast Track designation does not assure any such qualification or ultimate marketing approval by the FDA. In addition, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track designation does not provide assurance of ultimate FDA approval.

Because we are pursuing a variety of target indications for OP-1250, we may expend our limited resources to pursue a particular indication and fail to capitalize on indications or additional product candidates that may be more profitable or for which there is a greater likelihood of success.

We are currently focused on pursuing a variety of target indications for OP-1250, and we have expended, and plan to continue to expend, significant resources to pursue these and other indications for OP-1250. In addition, we may in the future spend our resources on other research programs and product candidates for specific indications that ultimately do not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights.

Because we have limited financial and managerial resources, we must focus our research and development efforts on those product candidates and specific indications that we believe are the most promising. As a result, we may forego or delay pursuit of opportunities with other product candidates or other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities, which will significantly harm our business, financial condition, results of operations and prospects.

Even if approved, OP-1250 may not achieve adequate market acceptance among physicians, patients, healthcare payors and others in the medical community necessary for commercial success.

Even if OP-1250 receives regulatory approval, it may not gain adequate market acceptance among physicians, patients, healthcare payors and others in the medical community. The degree of market acceptance would depend on a number of factors, including:

- the efficacy and safety profile as demonstrated in clinical trials compared to alternative treatments;
- the timing of market introduction of the product candidate as well as competitive products;
- the clinical indications for which the product candidate is approved;

- restrictions on the use of OP-1250, such as boxed warnings or contraindications in labeling, or a REMS, if any, which may not be required of alternative treatments and competitor products;
- the potential and perceived advantages of product candidates over alternative treatments;
- the cost of treatment in relation to alternative treatments;
- our pricing and the availability of coverage and adequate reimbursement by third-party payors, including government authorities;
- the availability of OP-1250 for use as a combination therapy;
- relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the effectiveness of sales and marketing efforts;
- unfavorable publicity relating to OP-1250 or similar approved products or product candidates in development by third parties; and
- the approval of other new therapies for the same indications.

If OP-1250 is approved but does not achieve an adequate level of acceptance by physicians, hospitals, healthcare payors and patients, we may not generate or derive sufficient revenue and could significantly harm our business, financial condition, results of operations and prospects.

If we experience delays or difficulties in the enrollment and/or maintenance of patients in clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

Patient enrollment is a significant factor in the timing of clinical trials, and the timing of our clinical trials depends, in part, on the speed at which we can recruit patients to participate in our trials, as well as completion of required follow-up periods. We may not be able to initiate or continue clinical trials for OP-1250, or any future product candidate we may develop, if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials to such trial's conclusion as required by the FDA, EMA or other comparable foreign regulatory authorities. Additionally, certain clinical trials for future product candidates may be focused on indications with relatively small patient populations, which may further limit enrollment of eligible patients or may result in slower enrollment than we anticipate. The eligibility criteria of our clinical trials, once established, may further limit the pool of available trial participants.

As a result of the COVID-19 pandemic, we have faced risk that enrollment of patients in our clinical trials and maintaining patients in our ongoing clinical trials could be delayed or limited as our clinical trial sites limit their onsite staff or temporarily close as a result of the COVID-19 pandemic, or are otherwise resource constrained, and may continue to face these risks as the COVID-19 pandemic continues to evolve. In addition, if, for any reason, patients are unable to visit clinical trial sites for dosing or data collection purposes related to the COVID-19 pandemic or for other reasons, such factors could delay the anticipated readouts from our clinical trials and ultimately delay future regulatory submissions. For instance, given industry wide COVID-19 impacts on clinical sites, we have experienced subject enrollment timeline delays in a Phase 1b clinical study of OP-1250 in combination with another CDK4/6 inhibitor and with a PI3K α inhibitor.

Patient enrollment may also be affected if our competitors have ongoing clinical trials for product candidates that are under development for the same indications as OP-1250, or any future product candidate we may

develop, and patients who would otherwise be eligible for our clinical trials instead enroll in clinical trials of our competitors' product candidates. Patient enrollment for any of our clinical trials may be affected by other factors, including:

- size and nature of the patient population;
- severity of the disease under investigation;
- availability and efficacy of approved drugs for the disease under investigation;
- patient eligibility criteria for the trial in question as defined in the protocol;
- perceived risks and benefits of the product candidate under study;
- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved for the indications we are investigating;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- proximity and availability of clinical trial sites for prospective patients;
- continued enrollment of prospective patients by clinical trial sites;
- the risk that patients enrolled in clinical trials will drop out of the trials before completion or, because they may be late-stage cancer patients, will not survive the full terms of the clinical trials; and
- the level of resources that clinical sites have to conduct a growing number of clinical studies.

Our inability to enroll and maintain a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for OP-1250 or any future product candidate we may develop and jeopardize our ability to obtain marketing approval for the sale of OP-1250 or any product candidate we may develop in the future. Furthermore, even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining enrollment of such patients in our clinical trials.

We intend to develop OP-1250, and may develop future product candidates, in combination with other therapies, which exposes us to additional risks.

We intend to develop OP-1250, and may develop other future product candidates, in combination with one or more other approved or unapproved therapies to treat cancer or other diseases. For example, in December 2021, we initiated a Phase 1b clinical study of OP-1250 in a combination trial with a cyclin-dependent kinase 4 and 6 inhibitor, and in the third quarter of 2022 we initiated Phase 1b clinical studies of OP-1250 in combination with another CDK4/6 inhibitor and with a PI3K α inhibitor.

Even if OP-1250, or any future product candidate we develop, were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risks that the FDA, EMA or comparable foreign regulatory authorities could revoke approval of the therapy used in combination with our product or that safety, efficacy, manufacturing or supply issues could arise with any of

those existing therapies. If the therapies we use in combination with OP-1250, or any future product candidate we may develop, are replaced as the standard of care for the indications we choose for OP-1250 or any future product candidate we may develop, the FDA, EMA or comparable foreign regulatory authorities may require us to conduct additional clinical trials. The occurrence of any of these risks could result in our own product, if approved, being removed from the market or being less successful commercially.

We also may choose to evaluate OP-1250 or future product candidates in combination with one or more cancer therapies that have not yet been approved for marketing by the FDA, EMA or comparable foreign regulatory authorities. We will not be able to market and sell OP-1250, or any future product candidate we may develop, in combination with an unapproved cancer therapy for a combination indication if that unapproved therapy does not ultimately obtain marketing approval either alone or in combination with our product. In addition, unapproved cancer therapies face the same risks described with respect to OP-1250 currently in development and clinical trials, including the potential for serious adverse effects, delay in their clinical trials and lack of FDA, EMA or comparable foreign regulatory approval.

If the FDA, EMA or comparable foreign regulatory authorities do not approve these other drugs or revoke their approval of, or if safety, efficacy, quality, manufacturing or supply issues arise with, the drugs we choose to evaluate in combination with OP-1250 or future product candidates we may develop, we may be unable to obtain approval of or market such combination therapy.

Risks associated with the in-licensing or acquisition of drug candidates could cause substantial delays in the preclinical and clinical development of our drug candidates.

We have previously in-licensed product candidates, and we may acquire or in-license potential product candidates for in the future, as we continue to build our pipeline. Such arrangements with third parties may impose diligence, development and commercialization obligations, milestone payments, royalty payments, indemnification and other obligations on us. Our obligations to pay milestone, royalty and other payments to our licensor may be substantial, and the amount and timing of such payments may impact our ability to progress the development and commercialization of our product candidate. Our rights to use any licensed intellectual property may be subject to the continuation of and our compliance with the terms of any such agreements.

Disputes over intellectual property and other rights that we have licensed or acquired, or may license or acquire in the future, from third parties could prevent or impair our ability to maintain any such arrangements on acceptable terms, result in delays in the commencement or completion of our preclinical studies and clinical trials and impact our ability to successfully develop and commercialize the affected product candidates. If we fail to comply with our obligations under any licensing agreements, these agreements may be terminated or the scope of our rights under them may be reduced and we might be unable to develop, manufacture or market any product that is licensed under these agreements.

The incidence and prevalence for target patient populations of OP-1250 are based on estimates and third-party sources. If the market opportunities for OP-1250, or any future product candidate we may develop, if and when approved, are smaller than we estimate or if any approval that we obtain is based on a narrower definition of the patient population, our revenue and ability to achieve profitability might be materially and adversely affected.

Periodically, we make estimates regarding the incidence and prevalence of target patient populations for particular diseases based on various third-party sources and internally generated analysis and use such estimates in making decisions regarding our drug development strategy, including acquiring or in-licensing product candidates and determining indications on which to focus in nonclinical or clinical trials.

The incidence and prevalence for target patient populations of OP-1250 are based on estimates and third-party sources. These estimates may be inaccurate or based on imprecise data. For example, the total addressable market opportunity will depend on, among other things, acceptance of our drugs by the medical community and patient access, drug pricing and reimbursement. The number of patients in the addressable markets may turn

out to be lower than expected, patients may not be otherwise amenable to treatment with our drugs, or new patients may become increasingly difficult to identify or gain access to. If the market opportunities for OP-1250, or any future product candidate we may develop, if and when approved, are smaller than we estimate or if any approval that we obtain is based on a narrower definition of the patient population, our revenue and ability to achieve profitability might be materially and adversely affected.

Interim, initial, “top-line” and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary or top-line data from our nonclinical studies and clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the top-line or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Top-line data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, top-line data should be viewed with caution until the final data are available.

From time to time, we may also disclose interim data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects. Further, disclosure of interim data by us has resulted and disclosure of interim data by us or by our competitors could in the future result in volatility in the price of our common stock.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of our particular program, the approvability or commercialization of our particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure.

If the interim, top-line, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, OP-1250 or any future product candidates we may develop may be harmed, which could significantly harm our business, financial condition, results of operations and prospects.

We face significant competition, and if our competitors develop and market technologies or products more rapidly than we do or that are more effective, safer or less expensive than OP-1250, or product candidates we may develop in the future, our commercial opportunities will be negatively impacted.

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary and novel products and product candidates. Our competitors have developed, are developing or may develop products, product candidates and processes competitive with OP-1250. Any product candidate that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. We believe that a significant number of products are currently under development, and may become commercially available in the future, for the treatment of conditions for which we are attempting to develop OP-1250. Products we may develop in the future are also likely to face competition from other products and therapies, some of which we may not currently be

aware. In addition, OP-1250 and any product candidate that we may develop in the future may need to compete with off-label drugs used by physicians to treat the indications for which we seek approval. This may make it difficult for us to replace existing therapies with OP-1250 and any product candidate that we may develop in the future.

In particular, there is intense competition in the field of women's cancer which we are pursuing. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, emerging and start-up companies, government agencies, universities and other research institutions. We also compete with these organizations to recruit management, scientists and clinical development personnel, which could negatively affect our level of expertise and our ability to execute our business plan. We will also face competition in establishing clinical trial sites, enrolling subjects for clinical trials and in identifying and in-licensing new product candidates.

If we are successful in developing OP-1250, it may compete against existing products and product candidates in development, to the extent any such product candidates are approved, for the treatment of estrogen receptor-positive, or ER+, breast cancer, including fulvestrant, marketed as Faslodex® by AstraZeneca PLC and or any generic equivalents of Faslodex® that are marketed or in development; elacestrant, marketed as ORSERDU™ by Stemline Therapeutics Inc.; giredestrant (GDC-9545), being developed by Roche Holding AG/Genentech, Inc.; camizestrant (AZD9833), being developed by AstraZeneca PLC; imlunestrant (LY3484356), being developed by Eli Lilly and Co.; ARV 471, being developed by Arvinas, Inc.; and lasofoxifene, being developed by Sermonix Pharmaceuticals.

We have chosen to initially address well-validated biochemical targets, and therefore expect to face competition from existing products and products in development. There are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. Many of these current and potential competitors may have significantly greater financial, manufacturing, commercial, clinical development, research and technical and human resources expertise than we do. Large pharmaceutical and biotechnology companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients and manufacturing biotechnology products. These companies also have significantly greater research and marketing capabilities than we do and may also have products that have been approved or are in late stages of development, and collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical and biotechnology companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product candidate that we develop obsolete. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies, as well as in acquiring technologies complementary to, or necessary for, our programs. As a result of all of these factors, our competitors may succeed in obtaining approval from the FDA, EMA or other comparable foreign regulatory authorities or in discovering, developing and commercializing products in our field before we do.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, have a broader label, are marketed more effectively, receive greater levels of reimbursement or are less expensive than products we may develop. Our competitors also may obtain marketing approval from the FDA, EMA or other comparable foreign regulatory authorities for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Even if OP-1250 or other product candidates we may develop in the future achieve marketing approval, they may be priced at a significant premium over competitive products if any have been approved by then, resulting in reduced competitiveness. Technological advances or products developed by our competitors may render our technologies or OP-1250 or product candidates we may develop in the future obsolete, less competitive or not economical. If we are unable to compete effectively, our opportunity to generate revenue from the sale of our product we may develop, if approved, would be adversely affected.

Changes in methods of OP-1250 manufacturing or formulation may result in additional costs or delay.

As OP-1250 progresses through nonclinical and clinical trials to marketing approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize yield and manufacturing batch size, minimize costs and achieve consistent quality and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause OP-1250 to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the altered materials. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of OP-1250 and jeopardize our ability to commercialize OP-1250, if approved, and generate revenue.

Any product candidate we develop may become subject to unfavorable third-party coverage and reimbursement practices, as well as pricing regulations.

The availability and extent of coverage and adequate reimbursement by third-party payors, including government health administration authorities, private health coverage insurers, managed care organizations and other third-party payors is essential for most patients to be able to afford expensive treatments. If we obtain marketing approval of OP-1250, or any future product candidate we may develop, sales of such product will depend substantially, both in the United States and internationally, on the extent to which the costs of the product will be covered and reimbursed by third-party payors. If reimbursement is not available, or is available only at inadequate levels, we may not be able to successfully commercialize OP-1250 or any future product candidates we may develop. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize an adequate return on our investment. Coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we may not successfully commercialize any product candidate for which we obtain marketing approval.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved products. In the United States, for example, principal decisions about reimbursement for new products are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or HHS. CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare, and private third-party payors often follow CMS's decisions regarding coverage and reimbursement to a substantial degree. However, one third-party payor's determination to provide coverage for a product candidate does not assure that other payors will also provide coverage for the product candidate. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. As a result, the coverage determination process is often time-consuming and costly. This process will require us to provide scientific and clinical support for the use of our product to each third-party payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular products and requiring substitutions of generic products and/or biosimilars. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Further, such payors are increasingly examining the medical necessity and reviewing the cost effectiveness of medical product candidates. There may be especially significant delays in obtaining coverage and reimbursement for newly approved drugs. Third-party payors may limit coverage to specific product candidates on an approved list, known as a formulary, which might not include

all FDA- approved drugs for a particular indication. We may need to conduct expensive pharmaco-economic studies to demonstrate the medical necessity and cost effectiveness of our product. Nonetheless, OP-1250 or any future product candidates we may develop may not be considered medically necessary or cost effective. We cannot be sure that coverage and reimbursement will be available for any product that we commercialize and, if reimbursement is available, what the level of reimbursement will be.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as OP-1250 or any future product candidates we may develop. In many countries, particularly the countries of the European Union, medical product prices are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after a product receives marketing approval. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of OP-1250 or any future product candidates we may develop to other available therapies. In general, product prices under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for OP-1250 or any future product candidates we may develop. Accordingly, in markets outside the United States, the reimbursement for any product that we commercialize may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits.

If we are unable to establish or sustain coverage and adequate reimbursement for any product candidates that we commercialize from third-party payors, the adoption of those products and potential sales revenue would be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved. Coverage policies and third-party payor reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for a product for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Guidelines and recommendations published by various organizations can reduce the use of OP-1250 or any future product candidates we may develop.

Government agencies promulgate regulations and guidelines directly applicable to us and to OP-1250 or any future product candidates we may develop. In addition, professional societies, such as practice management groups, private health and science foundations and organizations involved in various diseases from time to time may also publish guidelines or recommendations to the healthcare and patient communities. Recommendations of government agencies or these other groups or organizations may relate to such matters as usage, dosage, route of administration and use of concomitant therapies. Recommendations or guidelines suggesting the reduced use of OP-1250 or any future product candidates we may develop or the use of competitive or alternative products as the standard of care to be followed by patients and healthcare providers could result in decreased use of OP-1250 or any future product candidates we may develop.

Risks related to regulatory approval and other legal compliance matters

We may be unable to obtain U.S. or foreign regulatory approvals and, as a result, may be unable to commercialize OP-1250 or any future product candidate we may develop.

OP-1250 is, and any product candidate we develop in the future will be, subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, approval, recordkeeping, reporting, labeling, storage, packaging, advertising and promotion, pricing, marketing and distribution of drugs. Rigorous nonclinical testing and clinical trials and an extensive regulatory approval process must be successfully completed in the United States and in many foreign jurisdictions before a new drug can be marketed. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. We cannot provide any assurance that OP-1250 or any product

candidate we may develop will progress through required clinical testing and obtain the regulatory approvals necessary for us to begin selling them.

We have not conducted, managed or completed large-scale or pivotal clinical trials nor managed the regulatory approval process with the FDA or any other regulatory authority. The time required to obtain approvals from the FDA and other regulatory authorities is unpredictable and requires successful completion of extensive clinical trials which typically takes many years, depending upon the type, complexity and novelty of the product candidate. The standards that the FDA, EMA or other comparable foreign regulatory authorities use when evaluating clinical trial data can, and often does, change during drug development, which makes it difficult to predict with any certainty how they will be applied. We may also encounter unexpected delays or increased costs due to new government regulations, including future legislation or administrative action, or changes in FDA, EMA or other comparable foreign regulatory authorities' policies during the period of drug development, clinical trials and FDA, EMA or other comparable foreign regulatory authorities' regulatory review.

Any delay or failure in seeking or obtaining required approvals would have a material and adverse effect on our ability to generate revenue from the particular product candidate for which we are developing and seeking approval. Furthermore, any regulatory approval to market a drug may be subject to significant limitations on the approved uses or indications for which we may market the drug or the labeling or other restrictions. In addition, the FDA has the authority to require a REMS as part of approving a NDA, or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug. These requirements or restrictions might include limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry. These limitations and restrictions may significantly limit the size of the market for the drug and affect reimbursement by third-party payors.

We may also become subject to numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials and manufacturing of OP-1250. The foreign regulatory approval process varies among countries, and generally includes all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Moreover, the time required to obtain approval may differ from that required to obtain FDA approval.

Our business entails a significant risk of product liability and if we are unable to obtain sufficient insurance coverage, such inability could significantly harm our business, financial condition, results of operations and prospects.

Our business exposes us to significant product liability risks inherent in the development, testing, manufacturing and marketing of therapeutic treatments. Product liability claims could delay or prevent completion of our development programs. If we succeed in marketing products, such claims could result in an FDA, EMA or other regulatory authority investigation of the safety and effectiveness of our product, our manufacturing processes and facilities or our marketing programs. The FDA, EMA or other regulatory authority investigations could potentially lead to a recall of our product or more serious enforcement action, limitations on the approved indications for which it may be used or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in decreased demand for our product, injury to our reputation, costs to defend the related litigation, a diversion of management's time and our resources and substantial monetary awards to trial participants or patients. We currently have product liability insurance that we believe is appropriate for our stage of development and may need to obtain higher levels prior to marketing OP-1250, if approved. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could significantly harm our business, financial condition, results of operations and prospects.

OP-1250 and any future product candidates we develop may cause significant adverse events, toxicities or other undesirable side effects when used alone or in combination with other approved products or investigational new drugs that may result in a safety profile that could inhibit regulatory approval, prevent market acceptance, limit their commercial potential or result in significant negative consequences.

As is the case with pharmaceuticals generally, it is likely that there may be side effects and adverse events associated with the use of OP-1250 or any future product candidates we may develop. For example, during the Phase 1a portion of our Phase 1/2 clinical study, three patients had grade 4 neutropenia attributed to study drug by the investigator, and two of these patients presented with fever and neutropenia. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by OP-1250 or any future product candidates we may develop could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, EMA or other comparable foreign regulatory authorities. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may significantly harm our business, financial condition, results of operations and prospects.

If OP-1250 or any future product candidates we may develop are associated with undesirable side effects or have unexpected characteristics in nonclinical studies or clinical trials when used alone or in combination with other approved products or investigational new drugs, we may need to interrupt, delay or abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Treatment-related side effects could also affect patient recruitment or the ability of enrolled subjects to complete a trial, or result in potential product liability claims. Any of these occurrences may prevent us from achieving or maintaining market acceptance of the affected product candidate and may significantly harm our business, financial condition, results of operations and prospects.

Patients in our ongoing and planned clinical trials may in the future suffer significant adverse events or other side effects not observed in our nonclinical studies or previous clinical trials. OP-1250 or any future product candidates we may develop, may be used as chronic therapies or be used in pediatric populations, for which safety concerns may be particularly scrutinized by regulatory agencies. In addition, if OP-1250 or any future product candidates we may develop, are used in combination with other therapies, OP-1250 or any future product candidates we may develop may exacerbate adverse events associated with the therapy and it may not be possible to determine whether it was caused by our product or the one with which it was combined. Patients treated with OP-1250 or any future candidates we may develop, may also be undergoing surgical, radiation and chemotherapy treatments, which can cause side effects or adverse events that are unrelated to OP-1250 or any future product candidates we may develop, but may still impact the success of our clinical trials. The inclusion of critically ill patients in our clinical trials may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using or due to the gravity of such patients' illnesses.

If significant adverse events or other side effects are observed in any of our current or future clinical trials, we may have difficulty recruiting patients to the clinical trials, patients may drop out of our trials, or we may be required to abandon the trials or our development efforts of that product candidate altogether. We, the FDA, competent authorities of EU Member States, other comparable regulatory authorities or an IRB may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage trials have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude the product candidate from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance due to its tolerability versus other therapies. Any of these developments could significantly harm our business, financial condition, results of operations and prospects. Further, if OP-1250 obtains marketing approval, toxicities associated with OP-1250 and not seen during clinical testing may also develop after such

approval and lead to a requirement to conduct additional clinical safety trials, additional contraindications, warnings and precautions being added to the drug label, significant restrictions on the use of the product or the withdrawal of the product from the market. We cannot predict whether OP-1250 will cause toxicities in humans that would preclude or lead to the revocation of regulatory approval based on nonclinical studies or early-stage clinical trials.

The FDA, EMA and other comparable foreign regulatory authorities may not accept data from trials conducted in locations outside of their jurisdiction.

We may choose to conduct international clinical trials in the future. The acceptance of study data by the FDA, EMA or other comparable foreign regulatory authority from clinical trials conducted outside of their respective jurisdictions may be subject to certain conditions. In cases where data from foreign clinical trials are intended to serve as the basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (1) the data are applicable to the United States population and United States medical practice; (2) the trials are performed by clinical investigators of recognized competence and pursuant to current GCP requirements; and (3) the FDA is able to validate the data through an on-site inspection or other appropriate means. Additionally, the FDA's clinical trial requirements, including the adequacy of the patient population studied and statistical powering, must be met. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA, EMA or any applicable foreign regulatory authority will accept data from trials conducted outside of its applicable jurisdiction. If the FDA, EMA or any applicable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in OP-1250 or any future product candidates we may develop not receiving approval for commercialization in the applicable jurisdiction.

Obtaining and maintaining regulatory approval of OP-1250, or any product candidate we develop in the future, in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of OP-1250, or any product candidate we develop in the future, in other jurisdictions.

Obtaining and maintaining regulatory approval of OP-1250, or any product candidate we develop in the future, in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction. For example, even if the FDA, EMA or other foreign regulatory authority grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion and reimbursement of the product candidate in those countries. However, a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the United States, including additional nonclinical studies or clinical trials as clinical trials conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our product is also subject to approval.

Obtaining foreign regulatory approvals and establishing and maintaining compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product in certain countries. If we or any future collaborator fail to comply with the regulatory requirements in international markets or fail to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of OP-1250, or any product candidate we develop in the future, will be harmed.

Even if OP-1250, or any product candidate we develop in the future, receives regulatory approval, it will be subject to significant post-marketing regulatory requirements and oversight.

Any regulatory approvals that we may receive for OP-1250, or any product candidate we develop in the future, will require the submission of reports to regulatory authorities and surveillance to monitor the safety and efficacy

of the product candidate, may contain significant limitations related to use restrictions for specified age groups, warnings, precautions or contraindications, and may include burdensome post-approval study or risk management requirements. For example, the FDA may require a REMS in order to approve OP-1250, which could entail requirements for a medication guide, physician training and communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA, EMA or applicable foreign regulatory authorities approve OP-1250 or any product candidate we develop in the future, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export and recordkeeping for OP-1250 will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as on-going compliance with cGMPs and GCP for any clinical trials that we conduct post-approval. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic, unannounced inspections by the FDA and other regulatory authorities for compliance with cGMP regulations and standards. If we or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facilities where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. In addition, failure to comply with FDA, EMA and other comparable foreign regulatory requirements may subject our company to administrative or judicially imposed sanctions, including:

- delays in or the rejection of product approvals;
- restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials;
- restrictions on the products, manufacturers or manufacturing process;
- warning letters;
- civil and criminal penalties;
- injunctions;
- suspension or withdrawal of regulatory approvals;
- product seizures, detentions or import bans;
- voluntary or mandatory product recalls and publicity requirements;
- total or partial suspension of production; and
- imposition of restrictions on operations, including costly new manufacturing requirements.

The occurrence of any event or penalty described above may inhibit our ability to commercialize OP-1250, or any product candidate we may develop in the future, and generate revenue and could require us to expend significant time and resources in response and could generate negative publicity.

The FDA's and other regulatory authorities' policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of OP-1250 or any product candidate we may develop in the future. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, and we may not achieve or sustain profitability.

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.

If OP-1250 or any future product candidate we may develop is approved for marketing, and we are found to have improperly promoted off-label uses of those products, we may become subject to significant liability. The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products, such as OP-1250 or any future product candidates we may develop, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for OP-1250 or any future product candidates we may develop, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label based on the physician's independent medical judgment. If we are found to have promoted such off-label uses, we may become subject to significant liability. The U.S. federal government has levied large civil and criminal fines against companies for alleged improper promotion of off-label use and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of OP-1250 or any future product candidates we may develop, if approved, we could become subject to significant liability, which would significantly harm our business, financial condition, results of operations and prospects.

Disruptions at the FDA, EMA, applicable foreign regulatory authorities, the U.S. Securities and Exchange Commission, or the SEC, and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could significantly harm our business, financial condition, results of operations and prospects.

The ability of the FDA, EMA or any applicable foreign regulatory authority to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes, and other events that may otherwise affect the FDA, EMA or any applicable foreign regulatory authority's ability to perform routine functions. Average review times at the agencies have fluctuated in recent years as a result and could be delayed by the COVID-19 pandemic or other factors. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, in recent years, including in 2018 and 2019, the U.S. government shut down several times and certain regulatory agencies, such as the FDA and the SEC, had to furlough critical employees and stop critical activities. Separately, in response to the COVID-19 pandemic, in March 2020, the FDA announced its intention to postpone most inspections of foreign and domestic manufacturing facilities and in July 2020 only restarted inspections on a risk-based basis. Regulatory authorities outside the United States have adopted similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Future government shutdowns or delays could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

We may attempt to secure approval from the FDA, EMA or comparable foreign regulatory authorities through the use of accelerated approval pathways. If we are unable to obtain such approval, we may be required to conduct additional nonclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary marketing approvals. Even if we receive accelerated approval from the FDA, EMA or comparable foreign regulatory authorities, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post-marketing requirements, the FDA, EMA or comparable foreign regulatory authorities may seek to withdraw any accelerated approval.

We may in the future seek an accelerated approval for OP-1250 or future product candidates we may develop. Under the accelerated approval program, the FDA may grant accelerated approval to a product candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is usually contingent on the sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. Third-party payors may refuse to provide coverage or reimbursement for the drug until the confirmatory studies are complete. Additionally, if such post-approval studies fail to confirm the drug's clinical benefit, the FDA may withdraw its approval of the drug.

Prior to seeking accelerated approval for OP-1250, we intend to seek feedback from the FDA and will otherwise evaluate our ability to seek and receive accelerated approval. There can be no assurance that after our evaluation of the feedback and other factors we will decide to pursue or submit an NDA for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that after subsequent FDA feedback we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, if we decide to submit an application for accelerated approval or receive an expedited regulatory designation (e.g., breakthrough therapy designation) for OP-1250, there can be no assurance that such submission or application will be accepted or that any expedited development, review or approval will be granted on a timely basis, or at all. The FDA or other comparable foreign regulatory authorities could also require us to conduct further studies prior to considering our application or granting approval of any type. A failure to obtain accelerated approval or any other form of expedited development, review or approval for OP-1250 would result in a longer time period to commercialization of such product candidate, could increase the cost of development of OP-1250 and could harm our competitive position in the marketplace.

We may face difficulties from changes to current regulations and future legislation.

Existing regulatory policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of OP-1250 or any future product candidates we may develop. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability.

For example, in March 2010, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, was passed, which substantially changed the way healthcare is financed by both the government and private insurers and continues to significantly impact the U.S. pharmaceutical industry. There have been executive, judicial and Congressional challenges to certain aspects of the ACA. For example, on June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the “individual mandate” was repealed by Congress. In addition, there have been a number of health reform initiatives by the Biden administration that have impacted the ACA. For example, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. The IRA also eliminates the “donut hole” under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost through a newly established manufacturer discount program. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. These changes included aggregate reductions to Medicare payments to providers of 2% per fiscal year, effective April 1, 2013, which, due to subsequent legislative amendments, will stay in effect until 2031, except for a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic, unless additional congressional action is taken. Under current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug’s average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. In addition, Congress is considering additional health reform measures. These laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on potential customers for our drugs, if approved, and accordingly, our business.

Moreover, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several presidential executive orders, Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products.

For example, at the federal level, in July 2021, the Biden administration released an executive order that included multiple provisions aimed at prescription drugs. In response to Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform. The plan sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. In addition, the IRA, among other things, (1) directs HHS to negotiate the price of certain high-expenditure single-source drugs and biologics covered under Medicare and (2) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions will take effect progressively starting in fiscal year 2023, although they may be subject to legal challenges. In addition, the Biden administration released an additional executive order on October 14, 2022, directing HHS to report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. It is currently unclear how the IRA will be implemented but is likely to have a significant impact on the pharmaceutical industry. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost

disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that the recent reform activity, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize OP-1250 or any future product candidates we may develop.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for biotechnology products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of OP-1250 or any future product candidates we may develop, if any, may be.

Our relationships with healthcare professionals, clinical investigators, CROs and third party payors in connection with our current and future business activities may be subject to federal and state healthcare fraud and abuse laws, false claims laws, transparency laws, government price reporting, and privacy and security laws (including health information privacy and security laws), which could expose us to, among other things, criminal sanctions, civil penalties, contractual damages, exclusion from governmental healthcare programs, reputational harm, administrative burdens and diminished profits and future earnings.

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of our product candidate for which we obtain marketing approval. Our current and future arrangements with healthcare professionals, clinical investigators, CROs, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we research, market, sell and distribute our product for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act;
- the federal false claims and civil monetary penalties laws, including the civil False Claims Act, which can be enforced by private citizens through civil whistleblower or qui tam actions, prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits, among other things, executing or attempting to execute a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, also imposes obligations, including mandatory contractual terms, on covered entities including certain covered healthcare providers, health plans, and healthcare clearinghouses and their respective business associates and covered subcontractors that perform services for them that involve the use, or disclosure of, individually identifiable health information with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to annually report to CMS information regarding payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, as well as information regarding ownership and investment interests held by physicians and their immediate family members. The information reported is publicly available on a searchable website, with disclosure required annually; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third-party payors, including private insurers.

Some state laws require biotechnology companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. Some state laws require biotechnology companies to report information on the pricing of certain drug products. Some state and local laws require the registration of pharmaceutical sales representatives.

We are subject to stringent and evolving U.S. and foreign laws, regulations, rules, contractual obligations, policies and other obligations related to data privacy and security. Failure to comply with such obligations could lead to regulatory investigations or actions; litigation; fines and penalties; disruptions of our business operations; reputational harm; loss of revenue or profits; and other adverse business consequences.

State and international laws govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. For instance, the collection and use of health data in the European Union is governed by the General Data Protection Regulation, or the GDPR, which extends the enforcement of European Union data protection law to non-European Union entities under certain conditions, tightens existing European Union data protection principles, creates new obligations for companies and new rights for individuals. In particular, the GDPR includes obligations and restrictions concerning the consent and rights of individuals to whom the personal data relates, the transfer of personal data out of the European Economic Area, or EEA, or the UK, security breach notifications and the security and confidentiality of personal data. Further, the UK has implemented legislation similar to the GDPR, including the UK Data Protection Act and the UK GDPR, which provides for fines of up to the greater of 17.5 million British Pounds or 4% of a company's worldwide turnover, whichever is higher.

In addition to introducing new data protection requirements in the EEA, the GDPR also established potential fines for noncompliant companies. Failure to comply with the GDPR may result in substantial fines up to the greater of €20 million or 4% of annual global revenue and other administrative penalties. Such fines are in addition to any civil litigation claims by data subjects. EEA data protection authorities may interpret the GDPR and national laws differently and impose additional requirements, which contributes to the complexity of processing personal data in or from the EEA or the UK. Guidance on implementation and compliance practices is often updated or otherwise revised. The GDPR may increase our responsibility and liability in relation to

personal data that we process, and we may be required to put in place additional mechanisms ensuring compliance with the GDPR.

In addition, we may be unable to receive and/or further transfer onwards personal data that is processed subject to the EU GDPR and/or UK GDPR, or certain other data privacy and security regimes, due to limitations on cross-border data flows and/or actual or de facto data localization requirements. In particular, the EU GDPR and UK GDPR significantly restrict the transfer of personal data to the United States and other countries whose privacy laws are considered 'inadequate' for the purposes of either or both of those regulations. Although there are currently various mechanisms that may be used to effect such cross-border transfers of personal data in compliance with the EU GDPR and UK GDPR, such as the European Commission's 'Standard Contractual Clauses' and the United Kingdom's 'International Data Transfer Agreement / Addendum', all such mechanisms are subject to legal challenges, and there is no assurance that we can always satisfy or rely on these mechanisms to lawfully effect cross-border transfers of personal data where required.

Other jurisdictions relevant to our operations may implement, or adopt stringent interpretations of, their own data localization and cross-border data transfer laws. If there is no lawful manner for us to effect or be the recipient of cross-border transfers of personal data in compliance with the EU GDPR and/or UK GDPR, and/or other applicable data privacy and security obligations, or if the requirements for a compliant transfer are too onerous, we could face significant adverse consequences, including the interruption or degradation of our operations, the need to relocate part of or all of our business or data processing activities to other jurisdictions at significant expense, increased exposure to regulatory actions, substantial fines and penalties, the inability to transfer data and work with partners, vendors and other third parties, and injunctions against our processing or transferring of personal data necessary to operate our business. Some European regulators have ordered certain companies to suspend or permanently cease certain transfers of personal data to recipients outside the EEA for allegedly violating the EU GDPR's cross-border data transfer limitations. Additionally, companies that transfer personal data to recipients outside of the EEA and/or UK to other jurisdictions, particularly to the United States, are subject to increased scrutiny from regulators individual litigants and activist groups.

In the United States, numerous federal and state laws and regulations, including state personal information laws, state data breach notification laws, and federal and state consumer protection laws and regulations govern the collection, use, disclosure and protection of personal information. For example, the California Consumer Privacy Act, or CCPA, went into effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal information of consumers or households. The CCPA gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. While there is currently an exception for protected health information that is subject to HIPAA and clinical trial regulations, as currently written, the CCPA may impact certain of our business activities and may increase our compliance costs and potential liability.

Additionally, California voters approved a new privacy law, the California Privacy Rights Act, or CPRA, which went into effect on January 1, 2023. The CPRA will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. In addition, other states have enacted or proposed data privacy laws. For example, Virginia, Colorado, Utah and Connecticut all passed comprehensive privacy laws that have or will go into effect in 2023. While some of these state laws, like the CCPA, exempt some data processed in the context of clinical trials, these laws demonstrate our vulnerability to the evolving regulatory environment related to personal information and make it difficult to predict the impact of such laws on our business or operations. Aspects of these state privacy statutes remain unclear, resulting in further legal uncertainty and potentially requiring us to modify our data practices and policies and to incur substantial additional costs and expenses in an effort to comply.

In addition to the foregoing, any breach of privacy laws or data security laws, particularly resulting in a significant security incident or breach involving the misappropriation, loss or other unauthorized use or disclosure of sensitive or confidential patient or consumer information, could have a material adverse effect on our business, reputation and financial condition. As a data controller (under the GDPR) or business (under the CCPA), we will be accountable for any third-party service providers we engage to process personal data on our behalf, including our CROs. We attempt to mitigate the associated risks but there is no assurance that privacy and security-related safeguards will protect us from all risks associated with the third-party processing, storage and transmission of such information.

New legislation proposed or enacted in Illinois, Massachusetts, Nevada, New Jersey, New York, Rhode Island, Washington and other states, and a proposed right to privacy amendment to the Vermont Constitution, imposes, or has the potential to impose, additional obligations on companies that process confidential, sensitive and personal information, and will continue to shape the data privacy environment nationally. State laws are changing rapidly and there is discussion in Congress of a new federal data protection and privacy law to which we would become subject if it is enacted. All of these evolving compliance and operational requirements may impose significant costs that are likely to increase over time, may require us to modify our data processing practices and policies, divert resources from other initiatives and projects, modify our data practices and policies, restrict our business operations, and could restrict the way products and services involving data are offered, all of which could significantly harm our business, financial condition, results of operations and prospects. Further, certain state laws may be more stringent or broader in scope, or offer greater individual rights, with respect to confidential, sensitive and personal information than federal, international or other state laws, and such laws may differ from each other, which may complicate compliance efforts. Any actual or perceived failure by us to comply with these laws, regulations, or other obligations may lead to significant fines, penalties, regulatory investigations, lawsuits, significant costs for remediation, damage to our reputation, or other liabilities.

Many statutory requirements involving privacy and security, both in the United States and abroad, include obligations for companies to notify individuals of security breaches involving certain personal information, which could result from breaches experienced by us or our third-party service providers. Laws in all 50 U.S. states and the District of Columbia require businesses to provide notice to consumers whose personal information has been disclosed as a result of a data breach. These laws are not consistent, and compliance in the event of a widespread data breach is difficult and may be costly. We also may be contractually required to notify customers or other counterparties of a security breach. Although we may have contractual protections with our third-party service providers, contractors and consultants, any actual or perceived security breach of our systems or our third-party service providers could harm our reputation and brand, expose us to potential liability or require us to expend significant resources on data security and in responding to any such actual or perceived breach. Any contractual protections we may have from our third-party service providers, contractors or consultants may not be sufficient to adequately protect us from any such liabilities and losses, and we may be unable to enforce any such contractual protections.

In addition to the possibility of fines, lawsuits, regulatory investigations, public censure, other claims and penalties, and significant costs for remediation and damage to our reputation, we could be materially and adversely affected if legislation or regulations are expanded to require changes in our data processing practices and policies or if governing jurisdictions interpret or implement their legislation or regulations in ways that negatively impact our business. Complying with these various laws could cause us to incur substantial costs or require us to change our business practices and compliance procedures in a manner adverse to our business. Any inability to adequately address data privacy or security-related concerns, even if unfounded, or to comply with applicable laws, regulations, standards and other obligations relating to data privacy and security, could result in additional cost and liability to us, harm our reputation and brand, damage our relationships with customers and have a material adverse effect on our business.

Efforts to ensure that our current and future business arrangements with third parties will comply with applicable healthcare laws and regulations will involve on-going substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations

or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations, contractual damages, reputational harm, diminished profits and future earnings and the curtailment or restructuring of our operations. Defending against any such actions can be costly, time-consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. Further, if any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Our employees, independent contractors, consultants, commercial collaborators, principal investigators, CROs, suppliers and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, consultants, commercial collaborators, principal investigators, CROs, suppliers and vendors may engage in misconduct or other improper activities. Misconduct by these parties could include failures to comply with FDA regulations, provide accurate information to the FDA, comply with federal and state health care fraud and abuse laws and regulations, accurately report financial information or data or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the health care industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by these parties could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct by these parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations, contractual damages, reputational harm, diminished profits and future earnings and the curtailment or restructuring of our operations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could significantly harm our business, financial condition, results of operations or prospects.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic

tort claims that may be asserted against us in connection with our storage or disposal of hazardous and flammable materials, including chemicals and biological materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or commercialization efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Our research and development activities could be affected or delayed as a result of possible restrictions on animal testing.

Certain laws and regulations require us to test our product candidate on animals before initiating clinical trials involving humans. Animal testing activities have been the subject of controversy and adverse publicity. Animal rights groups and other organizations and individuals have attempted to stop animal testing activities by pressing for legislation and regulation in these areas and by disrupting these activities through protests and other means. To the extent the activities of these groups are successful, our research and development activities may be interrupted, delayed or become more expensive.

Our business activities may be subject to the U.S. Foreign Corrupt Practices Act, or the FCPA, and similar anti-bribery and anti-corruption laws of other countries in which we operate, as well as U.S. and certain foreign export controls, trade sanctions, and import laws and regulations. Compliance with these legal requirements could limit our ability to compete in foreign markets and subject us to liability if we violate them.

As we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. Our business activities may be subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate. The FCPA generally prohibits companies and their employees and third party intermediaries from offering, promising, giving or authorizing the provision of anything of value, either directly or indirectly, to a non-U.S. government official in order to influence official action or otherwise obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls. Our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, hospitals owned and operated by the government, and doctors and other hospital employees would be considered foreign officials under the FCPA. Recently the SEC and Department of Justice have increased their FCPA enforcement activities with respect to biotechnology and pharmaceutical companies. There is no certainty that all of our employees, agents or contractors, or those of our affiliates, will comply with all applicable laws and regulations, particularly given the high level of complexity of these laws. Violations of these laws and regulations could result in fines, criminal sanctions against us, our officers or our employees, disgorgement, and other sanctions and remedial measures, and prohibitions on the conduct of our business. Any such violations could include prohibitions on our ability to offer our product in one or more countries and could materially damage our reputation, our brand, our international activities, our ability to attract and retain employees and our business.

In addition, our product and activities may be subject to U.S. and foreign export controls, trade sanctions and import laws and regulations. Governmental regulation of the import or export of our product, or our failure to obtain any required import or export authorization for our product, when applicable, could harm our international sales and adversely affect our revenue. Compliance with applicable regulatory requirements regarding the export of our product may create delays in the introduction of our product in international markets or, in some cases, prevent the export of our product to some countries altogether. Furthermore, U.S. export control laws and economic sanctions prohibit the shipment of certain products and services to countries, governments, and persons targeted by U.S. sanctions. If we fail to comply with export and import regulations and such economic sanctions, penalties could be imposed, including fines and/or denial of certain export privileges. Moreover, any new export or import restrictions, new legislation or shifting approaches in the enforcement or scope of existing

regulations, or in the countries, persons, or product targeted by such regulations, could result in decreased use of our product by, or in our decreased ability to export our product to existing or potential customers with international operations. Any decreased use of our product or limitation on our ability to export or sell access to our product would likely significantly harm our business, financial condition, results of operations and prospects.

Risks related to employee matters, managing our growth and other risks related to our business

The COVID-19 pandemic could adversely impact our business, including our nonclinical studies and clinical trials.

The COVID-19 pandemic and government measures taken in response have had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred; supply chains have been disrupted; facilities and production have been suspended; and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen. In response to the spread of COVID-19, we closed our offices and limited the number of staff in any given research and development laboratory. In March 2022, we fully re-opened our offices to all employees and continue to comply with protocols implemented by respective health authorities. However, we may close our offices again in the future. As a result of the COVID-19 pandemic, we experienced some delays in setting up our current Phase 1/2 clinical study and in clinical site initiation, including delays in recruiting clinical site investigators and clinical site staff. We also experienced subject enrollment timeline delays in a Phase 1b clinical study of OP-1250 in combination with another CDK4/6 inhibitor and with a PI3K α inhibitor. We may experience these or other continuing impacts of the COVID-19 pandemic in the future. Additionally, we may experience further disruptions that could severely impact our business, nonclinical studies and clinical trials, including:

- delays or difficulties in enrolling and retaining patients in our clinical trials;
- difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site data monitoring, due to the COVID-19 pandemic, employers and others or interruption of clinical trial subject visits and study procedures, which may impact the integrity of subject data and clinical study endpoints;
- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines;
- interruption of, or delays in receiving, supplies of OP-1250 from our CMOs, due to staffing shortages, production slowdowns or stoppages and disruptions in delivery systems;
- interruptions in nonclinical studies due to restricted or limited operations at our laboratory facility;
- limitations on employee resources that would otherwise be focused on the conduct of our nonclinical studies and clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people; and
- interruption or delays to our sourced discovery and clinical activities.

The COVID-19 pandemic continues to evolve. The extent to which the outbreak impacts our business, nonclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease and the duration of the pandemic in the United States and other countries, business closures or disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the disease.

Unfavorable U.S. and global macroeconomic and geopolitical conditions could adversely affect our business, financial condition and results of operations.

Our results of operations could be adversely affected by general conditions in the U.S. and global economies, the U.S. and global financial markets and adverse geopolitical and macroeconomic developments, including the COVID-19 pandemic and the ongoing conflict between Ukraine and Russia and related sanctions. U.S. and global market and economic conditions have been, and continue to be, disrupted and volatile due to many factors, including component shortages and related supply chain challenges, geopolitical developments such as the ongoing COVID-19 pandemic and the conflict between Ukraine and Russia and related sanctions, increasing inflation rates and the responses by central banking authorities to control such inflation, among others. General business and economic conditions that could affect our business, financial condition or results of operations include fluctuations in economic growth, debt and equity capital markets, liquidity of the global financial markets, the availability and cost of credit, investor and consumer confidence, and the strength of the economies in which we, our manufacturers and our suppliers operate.

A severe or prolonged global economic downturn could result in a variety of risks to our business. For example, inflation rates, particularly in the United States, have increased recently to levels not seen in years, and increased inflation may result in increases in our operating costs (including our labor costs), reduced liquidity and limits on our ability to access credit or otherwise raise capital on acceptable terms, if at all. In addition, the U.S. Federal Reserve has raised, and may again raise, interest rates in response to concerns about inflation, which, coupled with reduced government spending and volatility in financial markets may have the effect of further increasing economic uncertainty and heightening these risks. A weak or declining economy could also strain our manufacturers and other service providers in our supply chain, possibly resulting in supply disruption. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Our success is highly dependent on our ability to attract and retain highly skilled executive officers and employees.

To succeed, we must recruit, retain, manage and motivate qualified clinical, scientific, technical and management personnel, and we face significant competition for experienced personnel. We are highly dependent on the management, research and development, clinical, financial and business development expertise of our executive officers, as well as the other members of our scientific and clinical teams.

Furthermore, although we have employment offer letters with each of our executive officers, each of them may terminate their employment with us at any time. We do not maintain “key person” insurance for any of our executives or employees. If we do not succeed in attracting and retaining qualified personnel, particularly at the management level, it could adversely affect our ability to execute our business plan and harm our operating results. In particular, the loss of one or more of our executive officers could be detrimental to us if we cannot recruit suitable replacements in a timely manner. The competition for qualified personnel in the biotechnology field is intense and as a result, we may be unable to continue to attract and retain qualified personnel necessary for the future success of our business. We could in the future have difficulty attracting experienced personnel to our company and may be required to expend significant financial resources in our employee recruitment and retention efforts.

Many of the other biotechnology companies that we compete against for qualified personnel have greater financial and other resources, different risk profiles and a longer history in the industry than we do. They also may provide more diverse opportunities and better prospects for career advancement. Some of these

characteristics may be more appealing to high-quality candidates than what we have to offer. If we are unable to continue to attract and retain high-quality personnel, the rate and success at which we can discover, develop and commercialize OP-1250 or any other product candidate will be limited and the potential for successfully growing our business will be harmed.

If we are unable to establish sales or marketing capabilities or enter into agreements with third parties to sell or market OP-1250 or any product candidate we may develop in the future, we may not be able to successfully sell or market OP-1250 or any future product candidate we may develop that obtain regulatory approval.

We currently do not have, and have never had, a marketing or sales team. In order to commercialize any product candidates, if approved, we must build marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services for each of the territories in which we may have approval to sell or market OP-1250 or any future product candidate we may develop. We may not be successful in accomplishing these required tasks.

Establishing an internal sales or marketing team with technical expertise and supporting distribution capabilities to commercialize OP-1250 or any product candidate we may develop in the future will be expensive and time-consuming, and will require significant attention of our executive officers to manage. Any failure or delay in the development of our internal sales, marketing and distribution capabilities could adversely impact the commercialization of OP-1250 or any product candidate we may develop in the future that we obtain approval to market, if we do not have arrangements in place with third parties to provide such services on our behalf. Alternatively, if we choose to collaborate, either globally or on a territory-by-territory basis, with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems, we will be required to negotiate and enter into arrangements with such third parties relating to the proposed collaboration. If we are unable to enter into such arrangements when needed, on acceptable terms, or at all, we may not be able to successfully commercialize OP-1250 or any product candidate we may develop in the future which may receive regulatory approval or any such commercialization may experience delays or limitations. If we are unable to successfully commercialize our approved product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses.

We have never commercialized a product candidate before and may lack the necessary expertise, personnel and resources to successfully commercialize any products on our own or together with suitable collaborators.

We have never commercialized a product candidate, and we currently have no sales force, marketing or distribution capabilities. To achieve commercial success for a product candidate, which we may license to others, we will rely on the assistance and guidance of those collaborators. For any product candidates for which we retain commercialization rights, we will have to develop our own sales, marketing and supply organization or outsource these activities to a third party.

Factors that may affect our ability to commercialize OP-1250, or any future product candidate we may develop, on our own include recruiting and retaining adequate numbers of effective sales and marketing personnel, obtaining access to or persuading adequate numbers of physicians to prescribe OP-1250 or any future product candidates we may develop and other unforeseen costs associated with creating an independent sales and marketing organization. Developing a sales and marketing organization will be expensive and time-consuming and could delay the launch of OP-1250 or any future product candidate we may develop. We may not be able to build an effective sales and marketing organization. If we are unable to build our own distribution and marketing capabilities or to find suitable partners for the commercialization of OP-1250 or any future product candidate we may develop, we may not generate revenues from such product candidate or be able to reach or sustain profitability.

In order to successfully implement our plans and strategies, we will need to grow the size of our organization, and we may experience difficulties in managing this growth.

As of January 31, 2023, we had 86 employees, 83 of whom were full-time, including 53 employees engaged in research and development. In order to successfully implement our development and commercialization plans and strategies, and as we transition into operating as a public company, we expect to need additional managerial, operational, sales, marketing, financial and other personnel. Future growth would impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining and motivating additional employees;
- managing our internal development efforts effectively, including the clinical, FDA, EMA and other comparable foreign regulatory agencies' review process for OP-1250 and any other future product candidates we may develop, while complying with any contractual obligations to contractors and other third parties we may have; and
- improving our operational, financial and management controls, reporting systems and procedures.

In addition, we expect to be conducting multiple clinical trials of OP-1250 for several different indications concurrently. Given the small size of our organization, we may encounter difficulties managing multiple clinical trials at the same time, which could negatively affect our ability to manage growth of our organization, particularly as we take on additional responsibility associated with being a public company. Our future financial performance and our ability to successfully develop and, if approved, commercialize, OP-1250 and any other future product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain independent organizations, advisors and consultants to provide certain services, including key aspects of clinical development and manufacturing. We cannot assure you that the services of independent organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by third-party service providers is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain marketing approval of OP-1250 and any other future product candidates we may develop or otherwise advance our business. We cannot assure you that we will be able to manage our existing third-party service providers or find other competent outside contractors and consultants on economically reasonable terms, or at all.

If we are not able to effectively expand our organization by hiring new employees and/or engaging additional third-party service providers, we may not be able to successfully implement the tasks necessary to further develop and commercialize OP-1250 and any other future product candidates we may develop and, accordingly, may not achieve our research, development and commercialization goals.

Our internal computer systems, or those of any of our CROs, manufacturers, other contractors, consultants, collaborators, potential future collaborators, or other third parties (including service providers in our supply chain) may fail or suffer security or data privacy breaches or other unauthorized or improper access to, use of, or destruction of our proprietary or confidential data, employee data, or personal data, which could result in additional costs, loss of revenue, significant liabilities, harm to our brand and material disruption of our operations.

Despite the implementation of preventative and detective security measures, our internal computer systems and those of our current and any future CROs and other contractors, consultants, collaborators and third-party service providers that process our sensitive information (including personal information and personally identifiable data), are vulnerable to damage or interruption from a variety of sources, including computer

viruses, unauthorized access, intentional or accidental acts or omissions by those with authorized access, natural disasters, terrorism, war, telecommunication and electrical failure, and cybersecurity threats (including the deployment of harmful malware, ransomware, denial-of-service attacks, supply chain attacks, social engineering, and other means to affect service reliability and threaten the confidentiality, integrity, and availability of information). The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity, and sophistication of attempted attacks and intrusions from around the world have increased. We may not be able to anticipate all types of security threats, and we may not be able to implement preventive measures effective against all such security threats. We have in the past and may in the future be subject to security breaches. For instance, we have had company laptops containing corporate information stolen from company offices. The techniques used by cyber criminals change frequently, may not be recognized until launched, and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations, or hostile foreign governments or agencies.

If such an event were to occur or were alleged to have occurred and cause interruptions in our operations or result in the unauthorized acquisition of or access to personally identifiable information or individually identifiable health information, it could result in a material disruption or termination of our drug discovery and development programs and our business operations, whether due to a loss of our trade secrets, personal information, or other similar disruptions. Some of the federal, state and foreign government requirements include obligations of companies to notify individuals of security breaches involving particular personally identifiable information, which could result from breaches experienced by us or by our vendors, contractors, or organizations with which we have formed strategic relationships. Notifications and follow-up actions related to a security breach could impact our reputation, cause us to incur significant costs, including legal expenses and remediation costs and divert resources from other efforts. For example, in November 2021, we were alerted to falsified information circulating on social media relating to our planned poster presentation for the Phase 1 dose-escalation portion of the ongoing Phase 1/2 clinical study of OP-1250 at the San Antonio Breast Cancer Symposium. Additionally, the loss or compromise of clinical trial data from completed or future clinical trials could result in delays or revocation of our regulatory approval efforts and significantly increase our costs to recover or reproduce the lost data. We also rely on third parties to manufacture OP-1250, and similar events relating to their computer systems could also have a material adverse effect on our business. We may have insufficient recourse against such third parties, and we may have to expend significant resources to mitigate the impact of such an event, to develop and implement protections to prevent future events of this nature from occurring, and to address other related concerns or issues. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data, or inappropriate disclosure of confidential or proprietary information, we could be exposed to litigation and governmental investigations, the further development and commercialization of OP-1250 could be delayed, and we could be subject to significant fines or penalties for any noncompliance with certain state, federal and/or international privacy and security laws.

Our insurance policies may not be adequate to compensate us for the potential losses arising from any such disruption, failure or security breach. In addition, such insurance may not be available to us in the future on economically reasonable terms, or at all. Further, our insurance may not cover all claims made against us and could have high deductibles in any event, and defending a suit, regardless of its merit, could be costly and divert management attention.

EU drug marketing and reimbursement regulations may materially affect our ability to market and receive coverage for our product in the European member states.

We intend to seek approval to market OP-1250 in both the United States and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for OP-1250, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the European Union, the pricing of drugs is subject to governmental control and other market regulations which could put pressure on the pricing and usage of OP-1250. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate. In addition, market acceptance and sales of

OP-1250 will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for OP-1250 and may be affected by existing and future healthcare reform measures.

Much like the federal Anti-Kickback Statute prohibition in the United States, the provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the European Union. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of EU Member States, such as the UK Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

In addition, in most foreign countries, including a number of EU Member States, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing and reimbursement vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Reference pricing used by various EU Member States and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. A member state may approve a specific price for the medicinal product, or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. In some countries, we may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of OP-1250 to other available therapies in order to obtain or maintain reimbursement or pricing approval. There can be no assurance that any country that has price controls or reimbursement limitations for biopharmaceutical products will allow favorable reimbursement and pricing arrangements for our product. Historically, products launched in the European Union do not follow price structures of the United States and generally prices tend to be significantly lower. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if reimbursement of our product is unavailable or limited in scope or amount, our potential revenues from sales and the potential profitability of OP-1250 in those countries would be negatively affected.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations, and those of our suppliers, CMOs, CROs and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, public health pandemics or epidemics (including, for example, the outbreak of COVID-19), and other natural or man-made disasters or business interruptions, for which we are predominantly self-insured. The occurrence of any of these business disruptions could seriously harm our operations, increase our costs and expenses and significantly harm our business, financial condition, results of operations and prospects.

Our ability to develop OP-1250 or any future product candidates we may develop could be disrupted if our operations or those of our suppliers are affected by man-made or natural disasters or other business interruptions. Our corporate headquarters are located in California near major earthquake faults and fire zones. The ultimate impact on us, our significant suppliers and our general infrastructure of being located near major earthquake faults and fire zones and being consolidated in certain geographical areas is unknown, but our operations and business could suffer in the event of a major earthquake, fire or other natural disaster.

Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

Our net operating loss, or NOL, carryforwards could expire unused and be unavailable to offset future income tax liabilities because of their limited duration or because of restrictions under U.S. tax law. NOLs generated in tax years ending on or prior to December 31, 2017 are only permitted to be carried forward for 20 taxable years under applicable U.S. federal tax law. Under the Tax Act, as modified by the Coronavirus Aid, Relief, and Economic Security, or CARES Act, federal NOLs generated in tax years ending after December 31, 2017 may be carried forward indefinitely, but the deductibility of such federal NOLs may be limited to 80% of current year taxable income for tax years beginning on or after December 31, 2020. It is uncertain if and to what extent various states will conform to the Tax Act or the CARES Act.

In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an “ownership change” (generally defined as a cumulative change in our ownership by “5 percent shareholders” that exceeds 50 percentage points over a rolling three-year period), the corporation’s ability to use its pre-change NOLs and certain other pre-change tax attributes to offset its post-change income and taxes may be limited. Similar rules may apply under state tax laws. We may have experienced such ownership changes in the past, and we may experience ownership changes in the future as a result subsequent shifts in our stock ownership, some of which are outside our control. We have not conducted any studies to determine annual limitations, if any, that could result from such changes in the ownership. Our ability to utilize those NOLs could be limited by an “ownership change” as described above and consequently, we may not be able to utilize a material portion of our NOLs and certain other tax attributes, which could have a material adverse effect on our cash flows and results of operations.

A variety of risks associated with marketing OP-1250 or any future product candidate we may develop internationally could significantly harm our business, financial condition, results of operations and prospects.

We plan to seek regulatory approval of OP-1250 or any future product candidates we may develop outside of the United States and, accordingly, we expect that we will be subject to additional risks related to operating in foreign countries if we obtain the necessary approvals, including:

- differing regulatory requirements and reimbursement regimes in foreign countries;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the FCPA or comparable foreign regulations;

- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

These and other risks associated with our international operations may significantly harm our business, financial condition, results of operations and prospects.

Risks related to our intellectual property

Our success depends on our ability to protect our intellectual property and our proprietary technologies.

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection in the United States and other countries for OP-1250 and any future product candidates that we may develop and technologies related to their various uses. We generally seek to protect our proprietary position by, among other things, filing patent applications in the United States and abroad related to OP-1250, our proprietary technologies, and their manufacture and uses that are important to our business, as well as inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position. We may also seek to protect our proprietary position by acquiring or in-licensing relevant issued patents or pending applications from third parties. If we or our potential licensors are unable to obtain or maintain patent protection with respect to OP-1250, proprietary technologies and their uses, our business, financial condition, results of operations and prospects could be significantly harmed.

Pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless, and until, patents issue from such applications, and then only to the extent the issued claims cover the technology. There can be no assurance that our patent applications will result in additional patents being issued or that issued patents will afford sufficient protection against competitors with similar technology, nor can there be any assurance that the patents issued will not be infringed, designed around or invalidated by third parties.

Moreover, in the future, some of our owned patents and patent applications, or any future licensed patents or patent applications, may be co-owned with third parties. If we are unable to obtain exclusive licenses to any such co-owners' interest in such patents or patent applications, then such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners to enforce such patents against third parties, and such cooperation may not be provided to us.

Even issued patents may later be found invalid or unenforceable or may be modified or revoked in proceedings instituted by third parties before various patent offices or in courts. Thus, the degree of future protection for our proprietary rights is uncertain. Only limited protection may be available and may not adequately protect our rights or permit us to gain or keep any competitive advantage. These uncertainties and/or limitations in our ability to properly protect the intellectual property rights relating to OP-1250 or any future product candidates we may develop could significantly harm our business, financial condition, results of operations and prospects.

We cannot be certain that the claims in our U.S. pending patent applications, and corresponding international patent applications, will be considered patentable by the United States Patent and Trademark Office, or USPTO, courts in the United States or by the patent offices and courts in foreign countries, nor can we be certain that the claims in our issued patent(s) will not be found invalid or unenforceable if challenged.

The patent application process is subject to numerous risks and uncertainties, and there can be no assurance that we or any of our potential future collaborators will be successful in protecting OP-1250 or any future product candidates we may develop by obtaining and defending patents. These risks and uncertainties include the following:

- patent applications must be filed in advance of certain events (e.g., third party filings, certain sales or offers for sale, or other activities that might be legally deemed to be public disclosures) and we might not be aware of such events or otherwise might not succeed in filing applications before they occur;
- the USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process, the noncompliance with which can result in abandonment or lapse of a patent or patent application, and partial or complete loss of patent rights in the relevant jurisdiction;
- patent applications may not result in any patents being issued;
- patents may be challenged, invalidated, modified, revoked, circumvented, found to be unenforceable or otherwise may not provide any competitive advantage;
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of patent protection both inside and outside the United States; and
- countries other than the United States may have patent laws less favorable to patentees than those upheld by U.S. courts, allowing foreign competitors a better opportunity to create, develop and market competing product candidates.

The patent prosecution process is also expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner or in all jurisdictions where protection may be commercially advantageous. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection, for example, if patentable aspects are publicly disclosed, by us or a third party, such as by public use, sale or offer for sale, or publication.

In addition, although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, outside scientific collaborators, CROs, third-party manufacturers, consultants, advisors and other third parties, any of these parties may breach such agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Further, although we require our employees, commercial contractors, and certain consultants and investigators to enter into invention assignment agreements that grant us ownership of any discoveries or inventions made by them while in our employ, we cannot guarantee that we have entered into such agreements with each party, we cannot provide any assurances that all such agreements have been duly executed, and any of these parties may breach such agreements and claim ownership in intellectual property that we believe is owned by us. In addition, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our owned or any licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Should any of the above events occur, it could significantly harm our business, financial condition, results of operations and prospects.

If the scope of any patent protection we obtain is not sufficiently broad, or if we lose any of our patent protection, our ability to prevent our competitors from commercializing similar or identical product candidates would be adversely affected.

The patent positions of biopharmaceutical companies generally are highly uncertain, involve complex legal and factual questions for which important legal principles remain unsolved and have been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect OP-1250 or which effectively prevent others from commercializing competitive technologies and product candidates.

Moreover, the coverage claimed in a patent application can be significantly reduced before a patent is issued, and its scope can be reinterpreted after issuance. Legal standards relating to valid and enforceable claim scope are unsettled in the United States and elsewhere and disputes challenging or re-defining scope are common in the biopharmaceutical industry. Even if patent applications we own or in-license currently or in the future issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage. Any patents that we own or in-license may be challenged or circumvented by third parties or may be narrowed or invalidated as a result of challenges by third parties. Consequently, we do not know whether OP-1250 or any future product candidates we may develop will be protectable or remain protected by valid and enforceable patents. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner which could significantly harm our business, financial condition, results of operations and prospects.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad.

The process by which patent applications are examined and considered for issuance as patents involves consideration by the relevant patent office of “prior art” relative to the invented technology. Different countries have different rules about what information or events can be considered “prior art,” and different requirements regarding when a patent application must be filed relative to any particular piece of potential prior art. Moreover, legal decisions can re-interpret or change whether particular information or events are considered to be “prior art.” Still further, in the United States, patent applicants are required to notify the USPTO of any material “prior art” of which they are aware for the patent examiner to consider in addition to independent searches that the patent examiner is required to do. Also, in the United States and certain other jurisdictions, third parties are entitled to submit prior art to patent offices for consideration during examination.

We may not be aware of certain relevant prior art, may fail to identify or timely cite certain prior art, or may not be able to convince a patent examiner that our patent(s) should issue in light of the art. Also, we cannot be certain that all relevant art will be identified during examination of a patent application so that, even if a patent issues, it may be susceptible to challenge that it is not valid over art that was not considered during its examination.

We may be subject to a third-party pre-issuance submission of prior art to the USPTO or other jurisdictions, or become involved in post-grant challenges such as opposition, derivation, revocation, reexamination, post-grant review, or PGR, and inter partes review, or IPR, or other similar proceedings, or in litigation, challenging our patent rights, including by challenging the validity or the claim of priority of our patents. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our patent rights, allow third parties to commercialize OP-1250 or any future product candidates we may develop and compete directly with us, without payment to us. Such challenges may result in loss of patent rights, loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of OP-1250 or any future product candidates we may develop. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity

question, for example, we cannot be certain that there is no invalidating prior art, including art of which we were unaware, and art which was not raised during prosecution of any of our patent applications. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our technology or platform, or any product candidates that we may develop. Such a loss of patent protection would significantly impact our business, financial condition, results of operations and prospects. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop, or commercialize current or future product candidates or could embolden competitors to launch products or take other steps that could disadvantage us in the marketplace or draw us into additional expensive and time-consuming disputes. Should any of these events occur, it could significantly harm our business, financial condition, results of operations and prospects.

Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- we may not be able to detect infringement of our issued patents;
- others may be able to develop products that are similar to OP-1250, or any future product candidates we may develop, but that are not covered by the claims of the patents that we may in-license in the future or own;
- our competitors may seek or may have already obtained patents that will limit, interfere with or eliminate our ability to make, use and sell OP-1250 or any future product candidates we may develop;
- we, or our current or future collaborators or license partners, might not have been the first to make the inventions covered by the issued patents or patent application that we may in-license in the future or own;
- we, or our current or future collaborators or license partners, might be found not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that the pending patent applications we may in-license in the future or own will not lead to issued patents;
- it is possible that there are prior public disclosures that could invalidate our patents, or parts of our patents, for which we are not aware;
- issued patents that we hold rights to may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- issued patents may not have sufficient term or geographic scope to provide meaningful protection;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;

- we may not develop additional proprietary technologies that are patentable;
- the patents of others may have an adverse effect on our business; and
- we may choose not to file a patent in order to maintain certain trade secrets, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, it could significantly harm our business, financial condition, results of operations and prospects.

Our commercial success depends significantly on our ability to operate without infringing, misappropriating or otherwise violating the patents and other proprietary rights of third parties. Claims by third parties that we infringe, misappropriate or otherwise violate their proprietary rights may result in liability for damages or prevent or delay our developmental and commercialization efforts.

Our commercial success depends in part on avoiding infringement, misappropriation or other violations of the patents and proprietary rights of third parties. However, our research, development and commercialization activities may be subject to claims that we infringe, misappropriate or otherwise violate patents or other intellectual property rights owned or controlled by third parties. A finding by a court or administrative body that we infringe the claims of issued patents owned by third parties could preclude us from commercializing OP-1250 or any future product candidates we may develop.

Other entities may have or obtain patents or proprietary rights that could limit our ability to make, use, sell, offer for sale or import OP-1250 or any future product candidates we may develop and products that may be approved in the future, or impair our competitive position. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biopharmaceutical industry, including patent infringement lawsuits, and proceedings, such as oppositions, reexaminations, IPR proceedings and PGR proceedings, before the USPTO and/or corresponding foreign patent offices. In addition, many companies in intellectual property-dependent industries, including the biopharmaceutical industry, have employed intellectual property litigation as a means to gain an advantage over their competitors. Numerous third-party U.S. and foreign issued patents and pending patent applications may exist in the fields in which we are developing OP-1250 or any future product candidates we may develop. There may be third-party patents or patent applications with claims to compositions, formulations, methods of manufacture or methods for treatment related to the use or manufacture of OP-1250 or any future product candidates we may develop. For example, we are aware of certain third-party patent applications and patents in the United States and abroad that include disclosure of chemical structures sharing certain similarities with OP-1250. It is possible that one or more of such third parties could pursue patent claims or assert patent claims that allegedly encompass OP-1250.

It is possible that one or more organizations will hold patent rights to which we will need a license. If those organizations refuse to grant us a license to such patent rights on reasonable terms, we may be unable to develop, manufacture, market, sell and commercialize products or services or perform research and development or other activities covered by these patents. In the event that any of these patents were to issue and be asserted against us, we believe that we would have defenses against any such assertion, including that such patents are not valid. However, if such defenses to such assertion were unsuccessful, we could be liable for damages, which could be significant and include treble damages and attorneys' fees if we are found to willfully infringe such patents. We could also be required to obtain a license to such patents, which may not be available on commercially reasonable terms or at all. If we are unable to obtain such a license, we could be precluded from commercializing any product candidates that were ultimately held to infringe such patents.

As the biopharmaceutical industry expands and more patents are issued, the risk increases that OP-1250, or any future product candidates we may develop, may be subject to claims of infringement of the patent rights of third parties. Because patent applications are maintained as confidential for a certain period of time, until the relevant application is published, we may be unaware of third-party patents that may be infringed by

commercialization of OP-1250, or any future product candidates we may develop, and we cannot be certain that we were the first to file a patent application related to a product candidate or technology. Moreover, because patent applications can take many years to issue, there may be currently-pending patent applications that may later result in issued patents that OP-1250 or any future product candidates we may develop may infringe. In addition, identification of third-party patent rights that may be relevant to our technology is difficult because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. There is also no assurance that there is not prior art of which we are aware, but which we do not believe is relevant to our business, which may, nonetheless, ultimately be found to limit our ability to make, use, sell, offer for sale or import our products that may be approved in the future, or impair our competitive position. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Still further, we cannot rely on our experience that third parties have not so far alleged that we infringe their patent rights, as provisions of U.S. patent laws provide a safe harbor from patent infringement for therapeutic products under clinical development. If and when we submit an NDA that safe harbor will expire.

Any claims of patent infringement, misappropriation or other violations asserted by third parties would be time consuming and could:

- result in costly litigation that may cause negative publicity;
- cause development delays;
- prevent us from commercializing OP-1250 or any future product candidates we may develop;
- require us to develop non-infringing technology, which may not be possible on a cost-effective basis;
- subject us to significant liability to third parties; or
- require us to enter into royalty or licensing agreements, which may not be available on commercially reasonable terms, or at all, or which might be non-exclusive, which could result in our competitors gaining access to the same technology.

Any patent-related legal action against us claiming damages or seeking to enjoin commercial activities relating to our products, or processes could subject us to significant liability for damages, including treble damages if we were determined to willfully infringe, and require us to obtain a license to manufacture or market OP-1250 or any future product candidates we may develop. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. We cannot predict whether we would prevail in any such actions or that any license required under any of these patents would be made available on commercially acceptable terms, if at all. Moreover, even if we or a future strategic partner were able to obtain a license, the rights may be nonexclusive, which could result in our competitors gaining access to the same intellectual property. In addition, we cannot be certain that we could redesign OP-1250 or any future product candidates we may develop processes to avoid infringement, if necessary.

An adverse determination in a judicial or administrative proceeding, or the failure to obtain necessary licenses, could prevent us from developing and commercializing OP-1250 or any future product candidates we may develop, which could significantly harm our business, financial condition and operating results. In addition, intellectual property litigation, regardless of its outcome, may cause negative publicity and could prohibit us from marketing or otherwise commercializing OP-1250 and future product candidates and technologies.

Parties making claims against us may be able to sustain the costs of complex patent litigation more effectively than we can. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or administrative proceedings, there is a risk that some of our confidential

information could be compromised by disclosure. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have material adverse effect on our ability to raise additional funds or otherwise significantly harm our business, financial condition, results of operations and prospects.

We may not be successful in obtaining or maintaining necessary rights from third parties for that we identify as necessary for OP-1250 through acquisitions and in-licenses.

Because our development programs may in the future require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in-license, or use these third-party proprietary rights.

While we may have issued patents that cover OP-1250, it is possible that third parties may have blocking patents that prevent us from marketing, manufacturing or commercializing our own patented products and practicing our own patented technology.

We may be unsuccessful in acquiring or in-licensing compositions, methods of use, processes, or other intellectual property rights from third parties that we identify as necessary for practicing inventions claimed by our patents, including the manufacture, sale and use of OP-1250 and any future product candidates we may develop. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, which could significantly harm our business, financial condition, results of operations and prospects.

We may be involved in lawsuits to protect or enforce our patents, which could be expensive, time consuming and unsuccessful. Further, our issued patents could be found invalid or unenforceable if challenged in court.

Competitors or other third parties may infringe, misappropriate or otherwise violate our intellectual property rights. To prevent infringement or unauthorized use, we may be required to file infringement or other intellectual property claims, which can be expensive and time-consuming. In addition, in a patent infringement proceeding, a court may decide that a patent we may in-license in the future or own is not valid, is unenforceable, and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our owned patents or future in-licensed patents do not cover the technology in question. If we or any of our potential future collaborators were to initiate legal proceedings against a third party to enforce a patent directed at OP-1250 or any future product candidates we may develop, the defendant could counterclaim that our patent is invalid and/or unenforceable in whole or in part. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description, non-enablement, or obviousness-type double patenting. Grounds for an unenforceability assertion could include an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution.

The outcome following legal assertions of invalidity and/or unenforceability is unpredictable, and prior art could render our patent invalid. There is no assurance that all potentially relevant prior art relating to our patent and patent applications has been found. There is also no assurance that there is not prior art of which we are aware, but which we do not believe affects the validity or enforceability of a claim in our patent and patent applications, which may, nonetheless, ultimately be found to affect the validity or enforceability of a claim.

If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we may lose at least part, and perhaps all, of the patent protection on such product candidate. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Such a loss of patent protection would significantly harm our business, financial condition, results of operations and prospects.

Even if resolved in our favor, litigation or other legal proceedings relating to our intellectual property rights may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or other legal proceedings relating to our intellectual property rights, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation or other proceedings.

Should any of these events occur, it could significantly harm our business, financial condition, results of operations and prospects.

Intellectual property litigation may lead to unfavorable publicity that harms our reputation and causes the market price of our common shares to decline.

During the course of any intellectual property litigation, there could be public announcements of the initiation of the litigation as well as results of hearings, rulings on motions, and other interim proceedings in the litigation. If securities analysts or investors regard these announcements as negative, the perceived value of our existing products, programs or intellectual property could be diminished. Accordingly, the market price of shares of our common stock may decline. Such announcements could also harm our reputation or the market for our future products, which could significantly harm our business, financial condition, results of operations and prospects.

Derivation proceedings may be necessary to determine priority of inventions, and an unfavorable outcome may require us to cease using the related technology or to attempt to license rights from the prevailing party.

Derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party.

Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of derivation proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with such proceedings could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties or enter into development or manufacturing partnerships that would help us bring OP-1250 or any future product candidates to market. Should any of these events occur, it could significantly harm our business, financial condition, results of operations and prospects.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications or those of our licensors and the enforcement or defense of our issued patents or those of our licensors.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. In particular, under the Leahy-Smith Act, the United States transitioned in March 2013 to a “first inventor to file” system in which, assuming that other requirements of patentability are met, the first inventor to file a patent application will be entitled to the patent regardless of whether a third party was first to invent the claimed invention. A third party that files a patent application in the USPTO after March 2013 but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Furthermore, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our technology and the prior art allow our technology to be patentable over the prior art. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we may not be certain that we or our licensors are the first to either (1) file any patent application related to OP-1250 or any future product candidate we may develop or (2) invent any of the inventions claimed in the patents or patent applications.

The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. These include allowing third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO-administered post-grant proceedings, including PGR, IPR and derivation proceedings. An adverse determination in any such submission or proceeding could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position.

Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. Thus, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications or those of our licensors and the enforcement or defense of our issued patents or those of our licensors, all of which could significantly harm our business, financial condition, results of operations and prospects.

Changes in U.S. patent law, or laws in other countries, could diminish the value of patents in general, thereby impairing our ability to protect OP-1250 or any future product candidates we may develop.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve a high degree of technological and legal complexity. Therefore, obtaining and enforcing biopharmaceutical patents is costly, time consuming and inherently uncertain. Changes in either the patent laws or in the interpretations of patent laws in the United States and other countries may diminish our ability to protect our inventions, obtain, maintain and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property. Such changes may also increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. We cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. In addition, Congress or other foreign legislative bodies may pass patent reform legislation that is unfavorable to us.

Further, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain

situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the U.S. federal courts, the USPTO, or similar authorities in foreign jurisdictions, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patent and the patents we might obtain or license in the future. Any of the foregoing could significantly harm our business, financial condition, results of operations, and prospects.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

It is possible that we do not perfect ownership of all patents, patent applications or other intellectual property. This possibility includes the risk that we do not identify all inventors, or identify incorrect inventors, which may lead to claims disputing inventorship or ownership of our patents, patent applications or other intellectual property by former employees or other third parties. There is also a risk that we do not establish an unbroken chain of title from inventors to us. Errors in inventorship or ownership can sometimes also impact priority claims. If we were to lose ability to claim priority for certain patent filings, intervening art or other events may preclude us from issuing patents.

Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Such an outcome could significantly harm our business, financial condition, results of operations and prospects. Even if we are successful in defending against such claims, litigation could result in substantial costs and distraction to management and other employees.

Patent terms may be inadequate to protect our competitive position on OP-1250 or any future product candidates we may develop for an adequate amount of time.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but there can be no assurance that any such extensions will be obtained, and the life of a patent, and the protection it affords, is limited. Even if patents covering OP-1250 or any future product candidates we may develop are obtained, once the patent life has expired, we may be open to competition from competitive products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

In the United States, patent term can be adjusted due to delays that occur during examination of patent applications, which may extend the term of a patent beyond 20 years. There is a risk that we may take action that detracts from any accrued patent term adjustment.

It is necessary to pay certain maintenance fees, also referred to as annuities or renewal fees in some countries, throughout the lifetime of a patent at regular intervals. Failure to pay these fees can cause a granted patent to prematurely expire, without an opportunity for revival. There is a risk that we may be unable to maintain patent protection for certain patents in all markets due to finite availability of resources. Any of the foregoing could significantly harm our business, financial condition, results of operations and prospects.

If we do not obtain patent term extension for OP-1250 or any future product candidates we may develop, our business, financial condition, results of operations and prospects may be significantly harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of OP-1250 or any future product candidates we may develop, one or more of our U.S. patents or those of our licensors may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, or the

Hatch- Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. A maximum of one patent may be extended per FDA approved product as compensation for the patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only those claims covering such approved drug product, a method for using it or a method for manufacturing it may be extended. Patent term extension may also be available in certain foreign countries upon regulatory approval of OP-1250 or any future product candidates we may develop. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations and prospects could be significantly harmed. Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and nonclinical data and launch their product earlier than might otherwise be the case.

We will not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States may be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we will not be able to prevent third parties from practicing our inventions in all countries outside the United States or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These infringing products may compete with OP-1250 or any future product candidates we may develop, without any available recourse.

The laws of some other countries do not protect intellectual property rights to the same extent as the laws of the United States. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries. In addition, the legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biopharmaceuticals. As a result, many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. Because the legal systems of many foreign countries do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceutical products, it could be difficult for us to stop the infringement, misappropriation or violation of our patents or our licensors' patents or marketing of competing products in violation of our proprietary rights. Proceedings to enforce our intellectual property and other proprietary rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents or the patents of our licensors at risk of being invalidated or interpreted narrowly, could put our patent applications or the patent applications of our licensors at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially

diminish the value of such patent. If we are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be significantly harmed.

Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment, and other requirements imposed by regulations and governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to the USPTO and various foreign patent offices at various points over the lifetime of our patents and/or patent applications. We have systems in place to remind us to pay these fees, and we rely on our outside patent annuity service to pay these fees when due. Additionally, the USPTO and various foreign patent offices require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with rules applicable to the particular jurisdiction. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. If such an event were to occur, potential competitors might be able to enter the market with similar or identical products or technology, which could significantly harm our business, financial condition, results of operations and prospects.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business, financial condition, results of operations and prospects could be significantly harmed.

We intend to use registered or unregistered trademarks or trade names to brand and market ourselves and our products. Our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively, and our business, financial condition, results of operations and prospects may be significantly harmed. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could significantly harm our business, financial condition, results of operations and prospects.

If we are unable to protect the confidentiality of our trade secrets, our business, financial condition, results of operations, prospects and competitive position would be significantly harmed.

In addition, we rely on the protection of our trade secrets, including unpatented know-how, technology and other proprietary information to maintain our competitive position. Although we have taken steps to protect our trade secrets and unpatented know-how, including entering into confidentiality agreements with third parties, and confidential information and inventions agreements with employees, consultants and advisors, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology or processes. Further, we cannot provide any assurances that all such agreements have been duly executed, and any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, or claim ownership in intellectual property that we believe is owned by us. Monitoring unauthorized uses and disclosures of our intellectual property is difficult, and we do not know whether the steps we have taken to protect our intellectual property will be effective. In

addition, we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets.

Moreover, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of these events occurs or if we otherwise lose protection for our trade secrets, the value of this information may be greatly reduced, and our competitive position would be harmed. If we do not apply for patent protection prior to such publication or if we cannot otherwise maintain the confidentiality of our proprietary technology and other confidential information, then our ability to obtain patent protection or to protect our trade secret information may be jeopardized. Any of the foregoing could significantly harm our business, financial condition, results of operations and prospects.

We may be subject to claims that we or our employees have wrongfully used or disclosed alleged confidential information or trade secrets.

We have entered into and may enter in the future into non-disclosure and confidentiality agreements to protect the proprietary positions of third parties, such as outside scientific collaborators, CROs, third-party manufacturers, consultants, advisors, potential partners, lessees of shared multi-company property and other third parties. Many of our employees and consultants were previously employed at, or may have previously provided or may be currently providing consulting services to, other biopharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants, and advisors do not use the proprietary information or know-how of others in their work for us, we may become subject to litigation where a third party asserts that we or our employees or consultants inadvertently or otherwise breached the agreements and used or disclosed trade secrets or other information proprietary to the third parties. Defense of such matters, regardless of their merit, could involve substantial litigation expense and be a substantial diversion of employee resources from our business. We cannot predict whether we would prevail in any such actions. Moreover, intellectual property litigation, regardless of its outcome, may cause negative publicity and could prohibit us from marketing or otherwise commercializing OP-1250 or any future product candidates or technologies we may develop. Failure to defend against any such claim could subject us to significant liability for monetary damages or prevent or delay our developmental and commercialization efforts, and cause us to lose valuable intellectual property rights or personnel, which could significantly harm our business, financial condition, results of operations and prospects. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to our management team and other employees.

Parties making claims against us may be able to sustain the costs of complex intellectual property litigation more effectively than we can. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise additional funds or otherwise significantly harm our business, financial condition, results of operations and prospects.

Our rights to develop and commercialize our technology and product candidate may be subject, in part, to the terms and conditions of licenses granted to us by others.

We may enter into license agreements in the future with others to advance our research or allow commercialization of OP-1250 or any future product candidates we may develop. These and other licenses may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in our licenses.

If we fail to comply with our obligations under any such license agreements, including obligations to make various milestone payments and royalty payments and other obligations, the licensor may have the right to terminate the license. If these agreements are terminated, we could lose intellectual property rights that are important to our business, be liable for any damages to such licensors or be prevented from developing and commercializing our product candidates, and competitors could have the freedom to seek regulatory approval of, and to market, products identical to ours. Termination of these agreements or reduction or elimination of our rights under these agreements may also result in our being required to negotiate new or reinstated agreements with less favorable terms, cause us to lose our rights under these agreements, including our rights to important intellectual property or technology, or impede, delay or prohibit the further development or commercialization of one or more product candidates that rely on such agreements. It is possible that we may be unable to obtain any additional licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis.

In addition, subject to the terms of any such license agreements, we may not have the right to control the preparation, filing, prosecution, maintenance, enforcement and defense of patents and patent applications covering the technology that we license from third parties. In such an event, we cannot be certain that these patents and patent applications will be prepared, filed, prosecuted, maintained, enforced and defended in a manner consistent with the best interests of our business, including the payment of all applicable fees for patents covering our product candidates. If our licensors fail to prosecute, maintain, enforce and defend such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated, and our right to develop and commercialize any of our products that are subject of such licensed rights could be adversely affected. Further, we may not be able to prevent competitors from making, using and selling competing products. In addition, even where we have the right to control the prosecution of patents and patent applications we have licensed to and from third parties, we may still be adversely affected or prejudiced by the actions or inactions of our licensees, our licensors and their counsel that took place prior to the date upon which we assumed control over patent prosecution.

Our licensors may have relied on third party consultants or collaborators or on funds from third parties such that our licensors are not the sole and exclusive owners of the patents we in-licensed. If other third parties have ownership rights to our in-licensed patents, they may be able to license such patents to our competitors, and our competitors could market competing products and technology. This could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

We may need to obtain additional licenses from existing licensors and others to advance our research or allow commercialization of product candidates we develop. It is possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could significantly harm our business, financial condition, results of operations and prospects significantly. We cannot provide any assurances that third party patents do not exist which might be enforced against our current technology, manufacturing methods, product candidates, or future methods or products resulting in either an injunction prohibiting our manufacture or future sales, or, with respect to our future sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties, which could be significant. Should any of these events occur, it could significantly harm our business, financial condition, results of operations and prospects.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

Disputes may arise between us and our past, current or future licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patents and other rights to third parties;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- our right to transfer or assign the license;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, the agreements under which we license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could significantly harm our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates, which could significantly harm our business, financial condition and prospects.

In spite of our best efforts, our licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to develop and commercialize products and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying patents fail to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. This could significantly harm our competitive position, business, financial condition and prospects.

Intellectual property discovered through government funded programs may be subject to federal regulations such as “march-in” rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights and limit our ability to contract with non-U.S. manufacturers.

We may develop, acquire, or license intellectual property rights that have been generated through the use of U.S. government funding or grants. Pursuant to the Bayh-Dole Act of 1980, the U.S. government has certain rights in inventions developed with government funding. These U.S. government rights include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right, under certain limited circumstances, to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (1) adequate steps have not been taken to commercialize the invention; (2) government action is necessary to meet public

health or safety needs; or (3) government action is necessary to meet requirements for public use under federal regulations (also referred to as “march-in rights”). If the U.S. government exercised its march-in rights in our future intellectual property rights that are generated through the use of U.S. government funding or grants, we could be forced to license or sublicense intellectual property developed by us or that we license on terms unfavorable to us, and there can be no assurance that we would receive compensation from the U.S. government for the exercise of such rights. The U.S. government also has the right to take title to these inventions if the grant recipient fails to disclose the invention to the government or fails to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us to expend substantial resources. In addition, the U.S. government requires that any products embodying any of these inventions or produced through the use of any of these inventions be manufactured substantially in the United States. This preference for U.S. industry may be waived by the federal agency that provided the funding if the owner or assignee of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. industry may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. Any exercise by the government of any of the foregoing rights could harm our competitive position, business, financial condition, results of operations and prospects.

Risks related to our dependence on third parties

We rely, and expect to continue to rely, on third parties, including independent clinical investigators and CROs, to conduct certain aspects of our nonclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties, comply with applicable regulatory requirements or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize OP-1250 or future product candidates we may develop and our business, financial condition, results of operations and prospects could be significantly harmed.

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct certain aspects of our nonclinical studies and clinical trials and to monitor and manage data for our ongoing nonclinical and clinical programs. We rely on these parties for execution of our nonclinical studies and clinical trials, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies and trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for OP-1250 in clinical development. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these third parties or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be adversely affected if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Further, these investigators and CROs are not our employees and we will not be able to control, other than by contract, the amount of resources, including time, which they devote to OP-1250 and clinical trials. These third parties may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities, which could affect their performance on our behalf. If independent investigators or CROs fail to devote sufficient resources to the development of OP-1250, or if CROs do not successfully carry out their contractual duties or obligations or

meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize OP-1250. As a result, our results of operations and the commercial prospects for OP-1250 would be harmed, our costs could increase and our ability to generate revenues could be delayed or precluded entirely, and our business, financial condition, results of operations and prospects could be significantly harmed.

Our CROs have the right to terminate their agreements with us in the event of an uncured material breach. In addition, some of our CROs have an ability to terminate their respective agreements with us if it can be reasonably demonstrated that the safety of the subjects participating in our clinical trials warrants such termination, if we make a general assignment for the benefit of our creditors or if we are liquidated.

The COVID-19 pandemic and government measures taken in response have also had a significant impact on our CROs, and we expect that they will face further disruption which may affect our ability to initiate and complete our nonclinical studies and clinical trials.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Additionally, CROs may lack the capacity to absorb higher workloads or take on additional capacity to support our needs. There can be no assurance that we will not encounter challenges or delays with CROs in the future or that these delays or challenges will not significantly harm our business, financial condition, results of operations and prospects.

We contract with third parties for the manufacture of OP-1250 for nonclinical studies and our ongoing clinical trials, and expect to continue to do so for additional clinical trials and ultimately for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of OP-1250 or other drugs necessary for the development or commercialization of OP-1250 or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not currently have the infrastructure or internal capability to manufacture supplies of OP-1250 for use in development and commercialization. We rely, and expect to continue to rely, on third-party manufacturers for the production of OP-1250 for nonclinical studies and clinical trials under the guidance of members of our organization. We do not have long-term supply agreements for OP-1250. Furthermore, the raw materials for OP-1250 are sourced, in some cases, from a single-source supplier. If we were to experience an unexpected loss of supply of OP-1250 for any reason, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience delays, disruptions, suspensions or terminations of, or be required to restart or repeat, any pending or ongoing clinical trials. For example, the extent to which the COVID-19 pandemic impacts our ability to procure sufficient supplies for the development of OP-1250 in the future will depend on the severity and duration of the spread of the virus, and the actions undertaken to contain COVID-19 or treat its effects.

We expect to continue to rely on third-party manufacturers for the commercial supply of OP-1250, if we obtain marketing approval. We may be unable to maintain or establish required agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the failure of the third party to manufacture OP-1250 according to our schedule, or at all, including if our third-party contractors give greater priority to the supply of other products over OP-1250 or otherwise do not satisfactorily perform according to the terms of the agreements between us and them;

- disruptions resulting from the impact of public health pandemics or epidemics (including, for example, the ongoing COVID-19 pandemic);
- the reduction or termination of production or deliveries by suppliers, or the raising of prices or renegotiation of terms;
- the termination or nonrenewal of arrangements or agreements by our third-party contractors at a time that is costly or inconvenient for us;
- the breach by the third-party contractors of our agreements with them;
- the failure of third-party contractors to comply with applicable regulatory requirements;
- the failure of the third party to manufacture OP-1250 according to our specifications;
- the mislabeling of clinical supplies, potentially resulting in the wrong dose amounts being supplied or active drug or placebo not being properly identified;
- clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions, or of drug supplies not being distributed to commercial vendors in a timely manner, resulting in lost sales; and
- the misappropriation of our proprietary information, including our trade secrets and know-how.

We do not have control over all aspects of the manufacturing process of, and are dependent on, our contract manufacturing partners for compliance with cGMP regulations for manufacturing both active drug substances and finished drug products. Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the United States. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA, EMA or others, they will not be able to secure and/or maintain marketing approval for their manufacturing facilities. In addition, we do not have control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA, EMA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of OP-1250, or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain marketing approval for or market OP-1250, if approved. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of OP-1250 or other drugs necessary for the development or commercialization of OP-1250 and significantly harm our business, financial condition, results of operations and prospects.

Furthermore, if the third-party providers of therapies or therapies in development used in combination with OP-1250 are unable to produce sufficient quantities for clinical trials or for commercialization of OP-1250, or if the cost of combination therapies are prohibitive, our development and commercialization efforts would be impaired, which would significantly harm our business, financial condition, results of operations and prospects. For example, for our Phase 1b clinical study of OP-1250 in combination with KISQALI® (ribociclib) or PIQRAY® (alpelisib), or the Novartis Study Drugs, in patients with metastatic ER+ breast cancer, we entered into a Clinical Collaboration and Supply Agreement with Novartis Institutes for BioMedical Research, Inc., or Novartis, or the Novartis Agreement. Under the terms of the Novartis Agreement, Novartis is providing KISQALI® (ribociclib) and PIQRAY® (alpelisib) for the clinical trial. If Novartis is unable to timely manufacture or provide KISQALI® (ribociclib) or PIQRAY® (alpelisib), or if the Novartis Agreement terminates and we are unable to obtain KISQALI® (ribociclib) or PIQRAY® (alpelisib) on the current terms, our Phase 1b clinical study may be delayed

and the cost to us to conduct this trial may significantly increase, which would significantly harm our business, financial condition, results of operations and prospects. For a description of the Novartis Agreement, see the section titled “Business - Clinical Trial Collaboration and Supply Agreement with Novartis” in our Annual Report on Form 10-K.

Our current and anticipated future dependence upon others for the manufacture of OP-1250 or other drugs necessary for the development or commercialization of OP-1250 may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis.

The manufacture of drugs is complex, and our third-party manufacturers may encounter difficulties in production. If any of our third-party manufacturers encounter such difficulties, our ability to provide adequate supply of OP-1250 for clinical trials or our product for patients, if approved, could be delayed or prevented.

Manufacturing drugs, especially in large quantities, is complex and may require the use of innovative technologies. Each lot of an approved drug product must undergo thorough testing for identity, strength, quality, purity and potency. Manufacturing drugs requires facilities specifically designed for and validated for this purpose, and sophisticated quality assurance and quality control procedures are necessary. Slight deviations anywhere in the manufacturing process, including filling, labeling, packaging, storage and shipping and quality control and testing, may result in lot failures, product recalls or spoilage. When changes are made to the manufacturing process, we may be required to provide nonclinical and clinical data showing the comparable identity, strength, quality, purity or potency of the products before and after such changes. If microbial, viral or other contaminations are discovered at the facilities of our manufacturer, such facilities may need to be closed for an extended period of time to investigate and remedy the contamination, which could delay clinical trials and significantly harm our business, financial condition, results of operations and prospects. The use of biologically derived ingredients can also lead to allegations of harm, including infections or allergic reactions, or closure of product facilities due to possible contamination. If our manufacturers are unable to produce sufficient quantities for clinical trials or for commercialization as a result of these challenges, or otherwise, our development and commercialization efforts would be impaired, which would significantly harm our business, financial condition, results of operations and prospects.

We have engaged in and may in the future engage in additional acquisitions, strategic partnerships or in-licensing opportunities, that may increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities, and subject us to other risks.

We have engaged in the past and may in the future engage in or evaluate various acquisition opportunities, strategic partnerships and in-licensing opportunities, including licensing or acquiring complementary products, intellectual property rights, technologies or businesses. Any potential acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of contingent liabilities;
- the issuance of our equity securities;
- assimilation of operations, intellectual property and products of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management’s attention from our existing programs and initiatives in pursuing such a strategic merger or acquisition;

- retention of key employees, the loss of key personnel and uncertainties in our ability to maintain key business relationships;
- risk of delay in receiving or the failure to receive anticipated benefits of any such transactions, or of facing unanticipated challenges;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or product candidates and marketing approvals; and
- our inability to generate revenue from acquired technology and/or products sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

In addition, if we undertake acquisitions or pursue partnerships or in-licensing opportunities in the future, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense. Moreover, we may devote substantial resources and fail to realize the anticipated benefits of such efforts, or we may incorrectly judge the value of an acquired or in-licensed product candidate, technology or other asset. Any such failure to realize the anticipated benefits of any or all of our acquisitions, strategic partnerships or in-licensing opportunities in the time frame expected, or at all, could result in additional costs or loss of revenue. Furthermore, we may not be able to locate suitable acquisition opportunities, and this inability could impair our ability to grow or obtain access to technology or products that may be important to the development of our business.

We have entered into collaborations with third parties for the development and commercialization of OP-1250. If those collaborations are not successful, we may not be able to capitalize on the market potential of OP-1250.

We have third-party collaborators for the development and commercialization of OP-1250. Our likely collaborators for any future collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies.

We have, and will likely continue to have, limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of OP-1250. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements. Collaborations involving OP-1250 could pose numerous risks to us, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations and may not perform their obligations as expected;
- collaborators may deemphasize or not pursue development and commercialization of OP-1250 or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus, including as a result of a sale or disposition of a business unit or development function, or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with OP-1250 if the collaborators believe that competitive products are more likely to be

successfully developed or can be commercialized under terms that are more economically attractive than ours;

- a collaborator with marketing and distribution rights to multiple products may not commit sufficient resources to the marketing and distribution of our product relative to other products;
- collaborators may not properly obtain, maintain, defend or enforce our intellectual property rights or may use our proprietary information and intellectual property in such a way as to invite litigation or other intellectual property related proceedings that could jeopardize or invalidate our proprietary information and intellectual property or expose us to potential litigation or other intellectual property related proceedings;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of OP-1250 or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates;
- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all; and
- if a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our drug development or commercialization program could be delayed, diminished or terminated.

If we decide to establish collaborations in the future but are not able to establish those collaborations on commercially reasonable terms, we may have to alter our development and commercialization plans.

Our drug development programs and the potential commercialization of OP-1250 or any future product candidates we may develop will require substantial additional cash to fund expenses. We may continue to seek to selectively form collaborations to expand our capabilities, potentially accelerate research and development activities and provide for commercialization activities by third parties. Any of these relationships may require us to incur non-recurring and other charges, increase our near and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business.

If we seek collaborations in the future, we will face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA, EMA or comparable foreign regulatory authorities, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing drugs, the existence of uncertainty with respect to our ownership of intellectual property and industry and market conditions generally. The potential collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for OP-1250 or any future product candidates we may develop. Further, we may not be successful in our efforts to establish a collaboration or other alternative arrangements for future product candidates because they may be deemed to be at too early of a stage of development for collaborative effort and third parties may not view them as having the requisite potential to demonstrate safety and efficacy.

In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. Even if we are successful in entering into a collaboration, the terms and conditions of that collaboration may restrict us from entering into future agreements on certain terms with potential collaborators.

If and when we seek to enter into additional collaborations, we may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop OP-1250 or any future product candidates we may develop or bring them to market and generate product revenue.

Risks related to ownership of our common stock

An active trading market for our common stock may not be sustained.

Our common stock is currently listed on The Nasdaq Global Select Market under the symbol “OLMA.” However, we cannot assure you that an active trading market for our common stock will be sustained. Accordingly, we cannot assure you of the liquidity of any trading market, your ability to sell your shares of our common stock when desired, or the prices that you may obtain for your shares. Further, an inactive market may also impair our ability to raise capital by selling our common stock and may impair our ability to enter into strategic partnerships or acquire businesses, products, or technologies using our common stock as consideration.

The price of our stock has been and may continue to be volatile, and you could lose all or part of your investment.

The trading price of our common stock has been and may continue to be highly volatile and subject to wide fluctuations in response to various factors, some of which we cannot control. For example, the closing price of our common stock from January 1, 2022 to March 3, 2023 has ranged from a low of \$2.04 to a high of \$9.43. The stock market in general, and pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies.

Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. In addition to the factors discussed in this “Risk Factors” section and elsewhere in this Annual Report, these factors include:

- the timing and results of nonclinical studies and clinical trials of OP-1250 or any future product candidates we may develop or those of our competitors;
- the success of competitive products or announcements by potential competitors of their product development efforts;
- regulatory actions with respect to our product candidate or our competitors’ products;
- actual or anticipated changes in our growth rate relative to our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;

- the recruitment or departure of key personnel;
- announcements by us or our competitors of significant acquisitions, strategic collaborations, joint ventures, collaborations or capital commitments;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- market conditions in the pharmaceutical and biotechnology sector;
- changes in the structure of healthcare payment systems;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our shares;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or our other stockholders; and
- general geopolitical, macroeconomic, industry and market conditions, including the COVID-19 pandemic and the ongoing conflict between Ukraine and Russia and related sanctions.

In addition, the trading prices for common stock of other biopharmaceutical companies have been highly volatile as a result of factors unrelated to the specific company or its technology, as well as due to the COVID-19 pandemic.

The realization of any of the above risks or any of a broad range of other risks, including those described in this “Risk Factors” section, could have a dramatic and adverse impact on the market price of our common stock.

Our quarterly operating results may fluctuate significantly or may fall below the expectations of investors or securities analysts, each of which may cause our stock price to fluctuate or decline.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- timing and variations in the level of expense related to the ongoing development of OP-1250 or future development programs;
- timing and status of enrollment for our clinical trials;
- impacts from the COVID-19 pandemic on us or third parties with which we engage;
- results of clinical trials, or the addition or termination of clinical trials or funding support by us or potential future partners;
- our execution of any collaboration, licensing or similar arrangements, and the timing of payments we may make or receive under potential future arrangements or the termination or modification of any such potential future arrangements;
- any intellectual property infringement, misappropriation or violation lawsuit or opposition, interference or cancellation proceeding in which we may become involved;

- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- if OP-1250 or any future product candidate we may develop receive regulatory approval, the timing and terms of such approval and market acceptance and demand for such product candidates;
- the timing and cost to establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval and intend to commercialize on our own or jointly with current or future collaborators;
- regulatory developments affecting OP-1250 or any future product candidate we may develop or those of our competitors; and
- changes in general market and economic conditions.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Our executive officers, directors, significant stockholders and their respective affiliates beneficially own a significant percentage of our common stock. Therefore, these stockholders are able to significantly influence us through this ownership position. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders. The interests of this group of stockholders may not always coincide with your interests or the interests of other stockholders and they may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock.

Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall.

Our common stock price could decline as a result of sales of a large number of shares of common stock or the perception that these sales could occur. These sales, or the possibility that these sales may occur, might also make it more difficult for us to sell equity securities in the future at a time and price that we deem appropriate.

As of December 31, 2022, we had 40,287,097 shares of common stock outstanding. Shares issued upon the exercise of stock options and warrants outstanding under our equity incentive plans or pursuant to future awards granted under those plans will become available for sale in the public market to the extent permitted by the provisions of applicable vesting schedules, and Rules 144 and 701 under the Securities Act.

Moreover, certain holders of shares of our common stock, have rights, subject to certain conditions, to require us to file registration statements covering the sale of their shares or to include their shares in registration statements that we may file for ourselves or our other stockholders. We also register the offer and sale of all

shares of common stock that we may issue under our equity compensation plans. Once we register the offer and sale of shares for the holders of registration rights and shares that may be issued under our equity incentive plans, these shares will be able to be sold in the public market upon issuance, subject to applicable securities laws.

In addition, in the future, we may issue additional shares of common stock, or other equity or debt securities convertible into common stock, in connection with a financing, acquisition, employee arrangement or otherwise. Any such issuance could result in substantial dilution to our existing stockholders and could cause the price of our common stock to decline.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to OP-1250 or future product candidates we may develop on unfavorable terms to us.

We may seek additional capital through a variety of means, including through public or private equity, debt financings or other sources, including up-front payments and milestone payments from strategic collaborations. To the extent that we raise additional capital through the sale of equity or convertible debt or equity securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. Such financing may result in dilution to stockholders, imposition of debt covenants, increased fixed payment obligations or other restrictions that may affect our business. If we raise additional funds through up-front payments or milestone payments pursuant to strategic collaborations with third parties, we may have to relinquish valuable rights to OP-1250 or future product candidates we may develop, or grant licenses on terms that are not favorable to us. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans.

We qualify as a “smaller reporting company” within the meaning of the Exchange Act and may take advantage of certain exemptions from disclosure requirements available to smaller reporting companies, which could make our securities less attractive to investors and may make it more difficult to compare our performance to the performance of other public companies.

Because our annual revenue was less than \$100.0 million during the most recently completed fiscal year and the market value of our voting and non-voting common stock held by non-affiliates was less than \$560.0 million measured on the last business day of our second fiscal quarter for the year ending December 31, 2022, we qualify again as a “smaller reporting company” as defined in the Exchange Act. We may take advantage of certain of the scaled disclosures available to smaller reporting companies including, among other things, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, or Section 404, presenting only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and presenting reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict whether investors will find our securities less attractive because we will rely on these exemptions. If some investors find our securities less attractive as a result of our reliance on these exemptions, the trading prices of our securities may be lower than they otherwise would be, there may be a less active trading market for our securities and the trading prices of our securities may be more volatile.

New or future changes to tax laws could materially adversely affect our company.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the United States recently passed the Inflation Reduction Act, which provides for a minimum tax equal to 15% of the adjusted financial statement income of certain large corporations, as well as a 1% excise tax on certain share buybacks by public corporations that would be imposed on such corporations. In addition, it is uncertain if and to what extent various states will conform to federal tax legislation. The impact of

such changes or future legislation could increase our U.S. tax expense and could have a material adverse impact on our business and financial condition.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws and Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Our amended and restated certificate of incorporation and amended and restated bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which holders of our common stock might otherwise receive a premium. These provisions also could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- prohibit our stockholders from calling a special meeting of our stockholders;
- prohibit cumulative voting;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a stockholder rights plan, or so-called “poison pill,” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 66 $\frac{2}{3}$ % of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our amended and restated certificate of incorporations or amended and restated bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, or DGCL, which prohibits a person who owns 15% or more of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired 15% or more of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware and the federal district courts of the United States will be the exclusive forums for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;
- any action asserting a claim of breach of fiduciary duty;
- any action asserting a claim against us arising under the DGCL, our amended and restated certificate of incorporation or our amended and restated bylaws; and
- any action asserting a claim against us that is governed by the internal-affairs doctrine or otherwise related to our internal affairs.

This provision would not apply to suits brought to enforce a duty or liability created by the Exchange Act. Furthermore, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our amended and restated certificate of incorporation further provides that the federal district courts of the United States will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our amended and restated certificate of incorporation. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions.

This exclusive-forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage lawsuits against us and our directors, officers and other employees. If a court were to find either exclusive-forum provision in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur further significant additional costs associated with resolving the dispute in other jurisdictions, all of which could seriously harm our business, financial condition, results of operations and prospects.

We do not currently intend to pay dividends on our common stock and, consequently, your ability to achieve a return on your investment will depend on appreciation of the value of our common stock.

We have never declared or paid any cash dividends on our equity securities. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to any appreciation in the value of our common stock, which is not certain.

General risk factors

The requirements of being a public company may strain our resources, result in more litigation and divert management's attention.

As a public company, we are subject to the reporting requirements of the Exchange Act, the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Stock Market LLC and other applicable securities rules and regulations. Complying with these rules and regulations has increased and will continue to increase our legal and financial compliance costs, make some activities more difficult, time consuming or costly and increase demand on our systems and resources. The Exchange Act requires, among other things, that we file annual, quarterly and current reports with respect to our business and operating results. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. We are required to disclose changes made in our internal control and procedures on a quarterly basis. In order to maintain and, if required, improve our disclosure controls and procedures and internal control over financial reporting to meet this standard, significant resources and management oversight may be required. As a result, management's attention may be diverted from other business concerns, which could significantly harm our business, financial condition, results of operations and prospects. We may also need to hire additional employees or engage outside consultants to comply with these requirements, which will increase our costs and expenses.

In addition, changing laws, regulations and standards relating to corporate governance and public disclosure are creating uncertainty for public companies, increasing legal and financial compliance costs and making some activities more time consuming. These laws, regulations and standards are subject to varying interpretations, in many cases due to their lack of specificity and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue-generating activities to compliance activities. If our efforts to comply with new laws, regulations and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to their application and practice, regulatory authorities may initiate legal proceedings against us and our business, financial condition, results of operations and prospects may be significantly harmed.

These rules and regulations may make it more expensive for us to obtain director and officer liability insurance and, in the future, we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These factors could also make it more difficult for us to attract and retain qualified members of our board of directors, particularly to serve on our audit committee and compensation committee, and qualified executive officers.

In addition, as a result of our disclosure obligations as a public company, our business and financial condition has become more visible, which we believe may result in threatened or actual litigation, including by competitors and other third parties. If those claims are successful, our business could be seriously harmed. Even if the claims do not result in litigation or are resolved in our favor, the time and resources needed to resolve them could divert our management's resources and seriously harm our business, financial condition, results of operations and prospects.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause

us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. For example, during August 2020, in connection with the preparation of our financial statements as of and for the years ended December 31, 2019 and 2018, we identified material weaknesses in our control over financial reporting. While we have remediated these material weaknesses and have implemented processes and controls over financial reporting to address the historical internal control deficiencies, there remains risk that future deficiencies may arise. Overall, we will continue with the implementation of additional measures around internal controls, and these will require validation and testing of the design and operating effectiveness of internal controls over a sustained period of financial reporting cycles. If we are unable to avoid future material weaknesses, our operations, financial reporting, or financial results could be harmed. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our stock.

If securities or industry analysts do not publish research or reports, or if they publish adverse or misleading research or reports, regarding us, our business or our market, our stock price and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that securities or industry analysts publish about us, our business or our market. If any of the analysts who cover us issue adverse or misleading research or reports regarding us, our business model, our intellectual property, our stock performance or our market, or if our operating results fail to meet the expectations of analysts, our stock price would likely decline. If one or more of these analysts cease coverage of us or fail to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

We may be subject to securities litigation, which is expensive and could divert management attention.

The market price of our common stock has been and may continue to be volatile and, in the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation and stockholder derivative actions. We may be the target of these types of litigation and claims in the future. These claims and litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business, financial condition, results of operations and prospects.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We designed our disclosure controls and procedures to reasonably assure that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well- conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 2. Properties.

Our corporate headquarters are located in San Francisco, California, where we lease approximately 15,000 square feet of office and laboratory space pursuant to lease agreements that expire between August 2023 and February 2026. We also lease a co-working space in Boston, Massachusetts. We believe that these existing facilities will be adequate for our near-term needs. If required, we believe that suitable additional or alternative space would be available in the future on commercially reasonable terms.

Item 3. Legal Proceedings.

From time to time, we may become involved in legal proceedings or be subject to claims arising in the ordinary course of our business. We are not currently a party to any material legal proceedings. Regardless of outcome, such proceedings or claims can have an adverse impact on us because of defense and settlement costs, diversion of resources and other factors, and there can be no assurances that favorable outcomes will be obtained.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities. Market Information

Our common stock has been listed on the Nasdaq Global Select Market under the symbol "OLMA" since November 19, 2020. Prior to that date, there was no public trading market for our common stock.

Holders of Record

As of the close of business on March 3, 2023, there were 59 stockholders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividends

We have never declared or paid cash dividends on our common stock. We currently intend to retain all available funds and future earnings, if any, to fund the development and expansion of our business, and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination regarding the declaration and payment of dividends, if any, will be at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Securities Authorized for Issuance under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Recent Sales of Unregistered Securities

None.

Issuer Purchases of Equity Securities

None.

Use of Proceeds from our Public Offering of Common Stock

In November 2020, our Registration Statement on Form S-1 (No. 333-249748) was declared effective by the SEC and we issued and sold an aggregate of 12,650,000 shares of common stock (inclusive of 1,650,000 shares of common stock pursuant to the underwriters' exercise of their option to purchase additional shares) at a public offering price of \$19.00 per share for aggregate net cash proceeds of approximately \$220.6 million, after deducting underwriting discounts, commissions and offering costs. No payments for such expenses were made directly or indirectly to (i) any of our officers or directors or their associates, (ii) any persons owning 10% or more of any class of our equity securities or (iii) any of our affiliates.

The sale and issuance of 12,650,000 shares in the IPO closed on November 23, 2020, J.P. Morgan Securities LLC, Jefferies LLC and Cowen and Company, LLC acted as joint book-running managers for the offering.

There has been no material change in the planned use of proceeds from the IPO from that described in the prospectus filed with the SEC pursuant to Rule 424(b)(4) under the Securities Act on November 19, 2020.

Item 6. Reserved.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following Management's discussion and analysis of our financial condition and results of operations should be read in conjunction with the consolidated financial statements and notes thereto included as part of this Annual Report. This discussion contains forward-looking statements that reflect our plans, estimates and beliefs and involve risks and uncertainties. Our actual results and the timing of certain events could differ materially from those anticipated in these forward-looking statements as a result of several factors, including those discussed in the section titled "Risk Factors" included under Part I, Item 1A and elsewhere in this Annual Report. See "Special Note Regarding Forward-Looking Statements" in this Annual Report.

Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of next generation targeted therapies for women's cancers. Our team has spent the past decade characterizing the structure and function of the estrogen receptor, or ER, a key driver of breast cancer in approximately 75% of patients, in order to develop more potent, oral therapies that completely inactivate this signaling pathway. Our lead product candidate, OP-1250, is a novel oral therapy with combined activity as both a complete ER antagonist, or CERAN, and a selective ER degrader, or SERD, which we believe will drive deeper, more durable responses than existing therapies. OP-1250, both as a monotherapy and in combination with inhibitors of cyclin-dependent kinase 4 and 6, or CDK4/6, demonstrated robust anti-tumor activity in a range of preclinical xenograft models of breast cancer, including in ESR1 and PIK3CA mutations and central nervous system, or CNS, metastasis. In August 2020, we initiated an ongoing Phase 1/2 monotherapy dose escalation and expansion study evaluating OP-1250 for the treatment of recurrent, locally advanced or metastatic ER-positive, or ER+, human epidermal growth factor receptor 2-negative, or HER2-, breast cancer. We reported initial data from the Phase 1a dose escalation portion of this study in November 2021, which provided proof-of-concept for OP-1250 as a monotherapy treatment for ER+/HER2- breast cancer. We reported additional monotherapy data from the Phase 1b dose expansion portion of this study in October 2022 and initiated the Phase 2 portion of the study. We anticipate presenting Phase 2 clinical data for OP-1250 as a monotherapy in the second half of 2023. In 2022, we also initiated Phase 1b/2 dose escalation and expansion studies evaluating OP-1250 in combination with cyclin-dependent kinase or CDK4/6 inhibitors palbociclib and ribociclib and phosphatidylinositol 3-kinase alpha, or PI3K α inhibitor, alpelisib. In December 2022, we reported initial data from the Phase 1a dose escalation portion of the study in combination with palbociclib which demonstrated combinability including no drug-drug interaction, or DDI, between the two agents. We anticipate presenting results from the Phase 2 clinical study for OP-1250 in combination with palbociclib in the second quarter of 2023 and from the Phase 1b clinical study for OP-1250 in combination with ribociclib in the second half of 2023. In July 2022, we were granted Fast Track designation from the FDA for OP-1250 for patients with ER+/HER2- metastatic breast cancer that has progressed following one or more lines of endocrine therapy with at least one line given in combination with a CDK4/6 inhibitor. Based on the clinical results we have achieved to date, we are advancing OP-1250 through to late stage clinical development both as a monotherapy and in combination with other targeted agents. We own worldwide development and commercialization rights to OP-1250. We believe OP-1250's oral formulation and dual mechanism of action directly address the limitations of current endocrine therapies, such as fulvestrant and tamoxifen, and position OP-1250 as a potential endocrine therapy of choice for the treatment of ER+ breast cancers. Our goal is to transform the standard of care for women living with cancers by developing more effective therapies that apply our deep understanding and collective expertise in endocrine-driven cancers, nuclear receptor activities and mechanisms of acquired resistance.

Since our inception, we have devoted substantially all of our resources to organizing and staffing our company, research and development activities, business planning, raising capital, establishing and maintaining our intellectual property portfolio, conducting nonclinical studies and clinical trials and providing general and administrative support for these operations.

We do not have any product candidates approved for commercial sale, and we have not generated any revenue from product sales. Our ability to generate product revenue sufficient to achieve profitability, if ever, will depend on the successful development and eventual commercialization of one or more of our product candidates which we expect, if it ever occurs, will take a number of years. We also do not own or operate, and currently have no plans to establish, any manufacturing facilities. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for nonclinical and clinical testing, as well as for commercial manufacturing if any of our product candidates obtain marketing approval. We believe that this strategy allows us to maintain a more efficient infrastructure by eliminating the need for us to invest in our own manufacturing facilities, equipment and personnel while also enabling us to focus our expertise and resources on the development of our product candidates.

As of December 31, 2022, we had cash, cash equivalents, and marketable securities of \$204.4 million. Based on our current operating plan, we believe that our cash, cash equivalents, and marketable securities as of December 31, 2022 will be sufficient to fund our planned operating expenses and capital expenditure requirements into 2025.

We have incurred significant operating losses since the commencement of our operations. Our net losses were \$104.8 million and \$71.1 million for the years ended December 31, 2022 and 2021, respectively. We expect to incur significant and increasing losses for the foreseeable future as we continue to advance our product candidate, make potential milestone payments to our licensors, and as we continue to operate as a public company. Our net losses may fluctuate significantly from period to period, depending on the timing of expenditures on our research and development activities. As of December 31, 2022, we had an accumulated deficit of \$209.0 million. Our primary use of cash is to fund operating expenses, which consist primarily of research and development expenditures and general and administrative expenditures. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and other current liabilities.

We expect to continue to incur net operating losses for at least the next several years, and we expect our research and development expenses, general and administrative expenses, and capital expenditures will continue to increase. We expect our expenses and capital requirements will increase significantly in connection with our ongoing activities as we:

- continue our ongoing and planned research and development of our lead product candidate, OP-1250, for the treatment of ER+ positive breast cancer;
- initiate nonclinical studies and clinical trials for any additional product candidates that we may pursue in the future;
- seek to discover and develop additional product candidates and further expand our clinical product pipeline;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- continue to scale up external manufacturing capacity with the aim of securing sufficient quantities to meet our capacity requirements for clinical trials and potential commercialization;
- establish a sales, marketing and distribution infrastructure to commercialize any approved product candidates and related additional commercial manufacturing costs;
- develop, maintain, expand, protect and enforce our intellectual property portfolio, including patents, trade secrets and know how;
- acquire or in-license other product candidates and technologies;

- attract, hire and retain additional clinical, scientific, quality control, and manufacturing management and administrative personnel;
- add clinical, operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts;
- expand our operations in the United States and to other geographies; and
- incur additional legal, accounting, investor relations and other expenses associated with operating as a public company.

We also expect to increase the size of our administrative function to support the growth of our business. Our net losses may fluctuate significantly from quarter-to-quarter and year-to-year, depending on the timing of our clinical trials, potential milestone payments to our licensors, and our expenditures on other research and development activities.

We will require substantial additional funding to develop our product candidate and support our continuing operations. Until such time that we can generate significant revenue from product sales or other sources, if ever, we expect to finance our operations through the sale of equity, debt financings or other capital sources, which could include income from collaborations, strategic partnerships or marketing, distribution, licensing or other strategic arrangements with third parties, or from grants. We may be unable to raise additional funds or to enter into such agreements or arrangements on favorable terms, or at all. Our ability to raise additional funds may be adversely impacted by potential worsening global economic conditions and the recent disruptions to, and volatility in, the credit and financial markets in the United States and worldwide resulting from geopolitical and macroeconomic events such as the COVID-19 pandemic and the ongoing conflict between Ukraine and Russia and related sanctions. Our failure to obtain sufficient funds on acceptable terms when needed could have a material adverse effect on our business, results of operations or financial condition, including requiring us to have to delay, reduce or eliminate our product development or future commercialization efforts. Insufficient liquidity may also require us to relinquish rights to product candidates at an earlier stage of development or on less favorable terms than we would otherwise choose. The amount and timing of our future funding requirements will depend on many factors, including the pace and results of our development efforts. We cannot provide assurance that we will ever be profitable or generate positive cash flow from operating activities.

The COVID-19 pandemic continues to evolve. As a result of the COVID-19 pandemic, we experienced some delays in setting up our current Phase 1/2 clinical study and in clinical site initiation, including delays in recruiting clinical site investigators and clinical site staff, which we may experience again in the future for clinical trials, including ongoing clinical trials involving OP-1250 in combination with other therapies. The extent of the impact of the COVID-19 pandemic on our business, operations, development timelines and plans, including the resulting impact on our expenditures and capital needs, remains uncertain, and will depend on factors, including the duration of the COVID-19 pandemic, frequency of outbreaks and the resultant impact on our development activities, planned clinical trial enrollment, future trial sites, CROs, third-party manufacturers, and other third parties with whom we do business, as well as its impact on regulatory authorities and our key scientific and management personnel. We continue to actively monitor the evolving situation related to the COVID-19 pandemic and may take further actions that alter our operations, including those that may be required by federal, state or local authorities, or that we determine are in the best interests of our employees and other third parties with whom we do business. During 2021 and 2022, although we modified our operations and practices due to the COVID-19 pandemic and to comply with federal, state and local requirements, our business, operations and development timelines were not materially adversely affected. In March 2022, we fully re-opened our offices to all employees and continue to comply with protocols implemented by respective health authorities. As a result of the COVID-19 pandemic, we experienced some delays in setting up our current Phase 1/2 clinical study and in clinical site initiation, including delays in recruiting clinical site investigators and clinical site staff. We also experienced subject enrollment timeline delays in a Phase 1b clinical study of OP-1250 in combination with another CDK4/6 inhibitor and with a PI3K α inhibitor. We may experience these or other continuing impacts of the COVID-19 pandemic in the future. We continue to monitor developments related to COVID-19 and may

close our offices again in the future. The extent to which the COVID-19 pandemic may affect our business, operations and development timelines and plans in the future, including the resulting impact on our expenditures and capital needs, remains uncertain.

In addition to the ongoing COVID-19 pandemic, global economic and business activities continue to face widespread macroeconomic uncertainties, including labor shortages, inflation and monetary supply shifts, recession risks and potential disruptions from the Russia-Ukraine conflict, all of which have resulted in volatility in the U.S. and global financial markets, and disruptions to trade, commerce, pricing stability, credit availability and supply chain continuity globally. The extent of the impact of these factors on our operational and financial performance, including our ability to execute our business strategies and initiatives in the expected time frame, will depend on future developments, which are uncertain and cannot be predicted. Any continued or renewed disruption resulting from these factors could negatively impact our business. We continue to monitor the impact of these macroeconomic factors on our results of operations, financial condition and cash flows.

Components of our results of operations

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of products for the foreseeable future.

Operating expenses

Research and development

Research and development expenses account for a significant portion of our operating expenses and consist primarily of external and internal expenses incurred in connection with the discovery and development of our product candidates. To date, our research and development expenses have related primarily to discovery efforts and nonclinical and clinical development of our product candidate OP-1250. Research and development expenses are recognized as incurred and payments made prior to the receipt of goods or services to be used in research and development are capitalized until the goods or services are received.

External expenses include:

- expenses incurred in connection with the discovery and nonclinical development of our product candidates, including under agreements with third parties, such as consultants and CROs;
- costs of manufacturing products for use in our nonclinical studies and clinical trials, including payments to CMOs and consultants;
- costs of funding research performed by third parties;
- costs of purchasing lab supplies and non-capital equipment used in designing, developing and manufacturing nonclinical study and clinical trial materials;
- costs associated with consultants for chemistry, manufacturing and controls development, regulatory, statistics and other services;
- expenses related to regulatory activities, including filing fees paid to regulatory agencies; and
- facility costs including rent, depreciation and maintenance expenses.

Internal expenses include employee and personnel-related costs and expenses, including salaries, benefits and stock-based compensation expense for employees and personnel engaged in research and development functions.

We expense research and development expenses in the periods in which they are incurred. Costs for certain activities, such as manufacturing and nonclinical studies and clinical trials, are generally recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and collaborators.

We typically use our employee, consultant and infrastructure resources across our development programs. We track outsourced development costs by product candidate or nonclinical program, but we do not allocate personnel costs, other internal costs or external consultant costs to specific product candidates or nonclinical programs.

Research and development expenses to advance the development of our lead product candidate and nonclinical program were \$82.3 million, and \$51.1 million for the years ended December 31, 2022, and 2021, respectively.

We expect our research and development expenses to increase substantially in absolute dollars for the foreseeable future as we advance OP-1250 or any other future product candidates we may develop into and through nonclinical studies and clinical trials and pursue regulatory approval of our product candidates. The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming. The actual probability of success for OP-1250 or any other future product candidates we may develop may be affected by a variety of factors including but not limited to: the safety and efficacy of our product candidates, early clinical data, investment in our clinical program, the ability of collaborators to successfully develop our licensed product candidates, competition, manufacturing capability and commercial viability. We may never succeed in achieving regulatory approval for our product candidates. As a result of the uncertainties discussed above, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenue from the commercialization and sale of our OP-1250 or any other future product candidates we may develop. Clinical and nonclinical development timelines, the probability of success and development costs can differ materially from expectations. We anticipate that we will make determinations as to which product candidates to pursue and how much funding to direct to each product candidate on an ongoing basis in response to the results of ongoing and future nonclinical studies and clinical trials, regulatory developments and our ongoing assessments as to each product candidate's commercial potential. In addition, we cannot forecast whether OP-1250 or any other future product candidates we may develop may be subject to future collaborations, when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development plans and capital requirements. We are also unable to predict when, if ever, we will generate revenue from our product candidates to offset these expenses. Our expenditures on current and future nonclinical and clinical development programs are subject to numerous uncertainties in timing and cost to completion. The duration, costs and timing of nonclinical studies and clinical trials and development of our product candidates will depend on a variety of factors, including:

- the timing and progress of nonclinical and clinical development activities;
- the number and scope of nonclinical and clinical programs we decide to pursue;
- our ability to maintain our current research and development programs and to establish new ones;
- establishing an appropriate safety profile with investigational new drug-enabling toxicology studies;
- successful patient enrollment in, and the initiation and completion of, clinical trials;

- the successful completion of clinical trials with safety, tolerability and efficacy profiles that are satisfactory to the FDA or any comparable foreign regulatory authority;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- receipt of regulatory approvals from applicable regulatory authorities;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- our ability to establish licensing or collaboration arrangements;
- the performance of our future collaborators, if any;
- development and timely delivery of commercial-grade product formulations that can be used in our planned clinical trials and for commercial launch;
- commercializing the product candidate, if approved, whether alone or in collaboration with others;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;
- obtaining, maintaining, defending and enforcing patent claims and other intellectual property rights;
- maintaining a continued acceptable safety profile of our products following approval; and
- obtaining and retaining key research and development personnel.

Any changes in the outcome of any of these factors could significantly impact the costs, timing and viability associated with the development of our product candidates.

General and administrative

General and administrative expenses consist primarily of personnel expenses, including salaries, benefits and stock-based compensation expense, for personnel in executive, finance, accounting, business development, legal, human resources, information technology, or IT, and administrative functions. General and administrative expenses also include costs not otherwise included in research and development expenses, including corporate facility costs, depreciation and other expenses, which include direct or allocated expenses for rent and maintenance of facilities and insurance, and professional fees for legal, patent and consulting services.

We expect that our general and administrative expenses will increase in the foreseeable future as we increase our headcount to support the continued research and development of our programs and the growth of our business. We also anticipate incurring additional expenses associated with operating as a public company, including increased expenses related to the building and improving of our IT infrastructure, including cyber security monitoring, legal, other regulatory and compliance, director and officer insurance, investor and public relations and tax-related services associated with maintaining compliance with the rules and regulations of the SEC and standards applicable to companies listed on a national securities exchange, additional insurance expenses, investor relations activities and other administrative and professional services.

Total other income

Total other income consists of interest income and other expenses. Interest income primarily consists of interest income on our cash equivalents and marketable securities. Other expense primarily consists of unrealized

foreign currency remeasurement gain (loss) and miscellaneous income (expense) not related to operating activities.

Results of operations

Comparison of the years ended December 31, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021:

	Year Ended December 31,		\$ Change
	2022	2021	
	(in thousands)		
Operating expenses:			
Research and development	\$ 82,274	\$ 51,100	\$ 31,174
General and administrative	24,714	20,391	4,323
Total operating expenses	<u>106,988</u>	<u>71,491</u>	<u>35,497</u>
Loss from operations	<u>(106,988)</u>	<u>(71,491)</u>	<u>(35,497)</u>
Other income (expense):			
Interest income	2,228	442	1,786
Other expense	(27)	(47)	20
Total other income	<u>2,201</u>	<u>395</u>	<u>1,806</u>
Net loss	<u>\$ (104,787)</u>	<u>\$ (71,096)</u>	<u>\$ (33,691)</u>

Research and development expenses

Research and development expenses for the year ended December 31, 2022 were \$82.3 million, compared to \$51.1 million for the year ended December 31, 2021. The increase of \$31.2 million was primarily due to increased spending in (i) advancing the clinical study for our lead product candidate OP-1250 and the associated contract manufacturing costs, (ii) other nonclinical research and discovery program costs, including the \$8.0 million upfront payment in connection with the Aurigene Agreement, and (iii) personnel-related costs due to increased headcount, including non-cash stock-based compensation expense increase of \$3.1 million.

General and administrative expenses

General and administrative expenses for the year ended December 31, 2022 were \$24.7 million, compared to \$20.4 million for the year ended December 31, 2021. The increase of \$4.3 million was primarily due to increased spending in (i) personnel-related expenses due to higher headcount, and (ii) public company-related costs, including legal compliance and other corporate costs.

Other income

Other income for the year ended December 31, 2022 was \$2.2 million, compared to \$0.4 million expense for the year ended December 31, 2021. The increase of \$1.8 million was primarily due to an increase in interest income from our marketable securities.

Liquidity and capital resources

Sources of liquidity

Since our inception, we have not generated any revenue from product sales and have incurred significant operating losses and negative cash flows from our operations. Our net losses were \$104.8 million and \$71.1 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had \$204.4 million in cash, cash equivalents and marketable securities and an accumulated deficit of \$209.0 million. We had no debt outstanding as of December 31, 2022. Through December 31, 2022, we had received aggregate gross proceeds of \$393.2 million from sales of our common stock, convertible preferred stock and

issuance of convertible promissory notes, stock option exercises, and the sale of stock through the 2020 Employee Stock Purchase Plan (“2020 ESPP”).

We expect to incur significant expenses and operating losses for the foreseeable future as we advance the clinical development of OP-1250 and other nonclinical research and development programs. We expect that our research and development and general and administrative costs will increase in connection with conducting clinical trials and additional nonclinical programs for our current and future research programs and product candidates, contracting with CMOs to support clinical trials and other nonclinical programs, expanding our intellectual property portfolio, and providing general and administrative support for our operations. As a result, we will need additional capital to fund our operations, which we may obtain from additional equity or debt financings, collaborations, licensing arrangements or other sources.

Our primary uses of cash are to fund our research and development activities, including with respect to OP-1250 and other nonclinical programs, business planning, establishing and maintaining our intellectual property portfolio, hiring personnel, raising capital and providing general and administrative support for these operations.

We currently have no financing commitments, such as lines of credit or guarantees, that are expected to affect our liquidity over the next five years.

Future funding and material cash requirements

To date, we have not generated any revenue from product sales. We do not expect to generate any meaningful revenue unless and until we obtain regulatory approval of and commercialize any of our product candidates, and we do not know when, or if at all, that will occur. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, continue or initiate clinical trials of, make potential milestone payments to our licensors, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for our product candidates, we expect to incur significant commercialization expenses related to program sales, marketing, manufacturing and distribution to the extent that such sales, marketing and distribution are not the responsibility of potential collaborators. Furthermore, we have incurred and expect to continue to incur additional costs associated with operating as a public company. The amount and timing of our future funding requirements will depend on many factors, including the pace and results of our development efforts.

We expect our cash, cash equivalents and marketable securities as of December 31, 2022 will enable us to fund our operating expenses and capital expenditure requirements into 2025 at which point we would need to obtain substantial additional funding in connection with our continuing operations.

The following table presents our material cash requirements for future periods:

(in thousands)	Material cash requirements due by period		
	Less than 1 year	More than 1 year	Total
Operating leases ⁽¹⁾	\$ 1,185	\$ 1,690	\$ 2,875

(1) We conduct our research and development programs internally and through third parties that include, among others, arrangements with vendors, consultants, CMOs, and CROs. We have contractual arrangements in the normal course of business with these parties, however, our contracts with them are cancelable generally on reasonable notice within one year and our obligations under these contracts are primarily based on services performed. We included certain contracts that have significant cancellation penalties and are material, which make the continuation of these arrangements reasonable.

In addition, under the Aurigene Agreement, we have payment obligations that are contingent upon future events such as the achievement of specified development, regulatory and commercial milestones. Financial terms of the Aurigene Agreement include potential future milestone payments of up to \$60.0 million in clinical development and regulatory milestones, and up to \$370.0 million in commercial milestones. Aurigene is also eligible to receive mid-single digit to the low double digit royalties on product sales, if any. The amount and timing of milestone obligations are unknown or uncertain as we are unable to estimate the timing or likelihood

of achieving the milestone events. Additionally, the amount of royalty payments are based upon future product sales, which we are unable to predict with certainty. These potential obligations are further described in Note 12 to our audited consolidated financial statements.

We also enter into contracts in the normal course of business with CROs and clinical sites for the conduct of clinical trials, non-clinical research studies, professional consultants for expert advice and other vendors for clinical supply manufacturing or other services. These contracts generally provide for termination on notice, and therefore are cancelable contracts.

If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of product discovery, nonclinical studies and clinical trials;
- the scope, prioritization and number of our research and development programs;
- the costs, timing and outcome of regulatory review of our product candidate;
- our ability to establish and maintain collaborations on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under any collaboration agreements we enter into;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under collaboration agreements, if any;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the extent to which we acquire or in-license other product candidates and technologies;
- the costs of securing manufacturing arrangements for commercial production; and
- the costs of establishing or contracting for sales and marketing capabilities if we obtain regulatory approvals to market our product candidates.

Identifying potential product candidates and conducting nonclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes many years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidate, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of a product candidate that we do not expect to be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Cash flows

The following table shows a summary of our cash flows for each of the periods presented:

(in thousands)	Year Ended December 31,	
	2022	2021
Net cash used in operating activities	\$ (82,065)	\$ (50,690)
Net cash provided by (used in) investing activities	91,479	(275,438)
Net cash provided by financing activities	476	1,391
Net increase (decrease) in cash and cash equivalents	\$ 9,890	\$ (324,737)

Operating activities

Net cash used in operating activities during the year ended December 31, 2022 consisted primarily of our net loss of \$104.8 million, partially offset by non-cash charges of \$18.4 million and a net increase of \$4.3 million in net operating assets and liabilities. The net loss consisted primarily of \$82.3 million in research and development expenses and \$24.7 million in general and administrative expenses. The non-cash charges consisted primarily of stock-based compensation of \$18.8 million, depreciation and amortization expenses of \$0.4 million, and non-cash lease expense of less than \$0.1 million, net of cash payments of \$1.3 million. These non-cash expenses were partially offset by net discount accretion on our marketable securities of \$0.8 million. The change in operating assets and liabilities was primarily due to (i) an increase of \$7.0 million in other current liabilities, and (ii) an increase of \$0.4 million in accounts payable, which is primarily resulted from timing of invoicing by vendors and related payments. The changes are partially offset by (i) an increase of \$2.0 million in prepaid expenses and other current assets, and (ii) an increase of \$1.1 million in other assets mostly due to vendor deposits paid for clinical studies.

Net cash used in operating activities during the year ended December 31, 2021 consisted primarily of our net loss of \$71.1 million, partially offset by non-cash charges of \$16.6 million and a net increase of \$3.8 million in net operating assets and liabilities. The net loss consisted primarily of \$51.1 million in research and development expenses and \$20.4 million in general and administrative expenses. The non-cash charges consisted primarily of stock-based compensation of \$15.9 million, depreciation and amortization expenses of \$0.4 million, and non-cash lease expense of \$0.2 million, net of cash payments of \$1.0 million. The change in operating assets and liabilities was primarily due to a net increase of \$0.1 million in other assets and prepaid expenses and other current assets related to advanced payments for corporate insurance and subscriptions and licenses, and a decrease of \$0.7 million in accounts payable, partially offset by an increase of \$4.6 million in accrued liabilities, primarily as a result of timing of receipts of invoices.

Investing Activities

Net cash provided by investing activities during the year ended December 31, 2022 was predominately due to maturities of marketable securities which was partially offset by the purchase of marketable securities.

Net cash used in investing activities during the year ended December 31, 2021 was predominately due to purchases of marketable securities which was financed through the proceeds from the IPO and convertible preferred stock sale, and purchases of equipment, partially offset by the maturities of marketable securities.

Financing activities

Net cash provided by financing activities during the year ended December 31, 2022 consisted of \$0.3 million and \$0.1 million in net proceeds from the sale of our common stock under the 2020 ESPP and the exercise of stock options, respectively.

Net cash provided by financing activities during the year ended December 31, 2021 consisted of \$0.7 million and \$0.7 million in net proceeds from the sale of our common stock under the 2020 ESPP and the exercise of stock options, respectively.

Critical accounting estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, expenses and the disclosure of our contingent liabilities in our consolidated financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 to our consolidated financial statements elsewhere in this Annual Report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our audited consolidated financial statements.

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing purchase orders and open contracts, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the services when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met; however, some require advance payments. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include the costs incurred for services performed by CROs and CMOs among others, in connection with research and development activities for which we have not yet been invoiced.

We contract with CROs and CMOs to conduct clinical and manufacturing and other research and development services on our behalf. We base our expenses related to CROs and CMOs on our estimates of the services received and efforts expended pursuant to quotes and contracts with them. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our CROs or CMOs will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or amount of prepaid expense accordingly. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts actually incurred.

Smaller reporting company

Because our annual revenue was less than \$100.0 million in 2022 and the market value of our voting and non-voting common stock held by non-affiliates was less than \$700.0 million measured on the last business day of our second fiscal quarter in 2022, we qualify as a “smaller reporting company” as defined in the Exchange Act. We took advantage of certain of the scaled disclosures available to smaller reporting companies including, among other things, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act (“Section 404”), presenting only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and presenting reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements.

Recently issued accounting pronouncements

See Note 2 to our consolidated financial statements contained in this Annual Report for a description of recent accounting pronouncements applicable to our consolidated financial statements.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest rate risk

We are exposed to market risks in the ordinary course of our business. These risks primarily include interest rate sensitivities. As of December 31, 2022 and 2021, we had cash, cash equivalents and marketable securities of \$204.4 million and \$287.3 million, respectively. We generally hold our cash in interest-bearing bank accounts and money market funds. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. An immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our cash, cash equivalents and marketable securities.

Financial institution risk

Substantially all of our cash is held with a single financial institution. Due to its size, this financial institution represents a minimal credit risk. Cash amounts held at financial institutions are insured by the Federal Deposit Insurance Corporation up to \$250,000.

Foreign currency exchange risk

Our expenses are generally denominated in U.S. dollars. To date, we have not had any significant foreign currency transactions, and we do not have a formal hedging program with respect to foreign currency. A 10.0% increase or decrease in current exchange rates would not have a material effect on our financial results.

Effects of inflation

Inflation generally affects us by increasing our cost of labor and research and development costs. We do not believe that inflation has had a material effect on our results of operations during the periods presented.

Item 8. Consolidated Financial Statements and Supplementary Data.

Olema Pharmaceuticals, Inc.
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Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Olema Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Olema Pharmaceuticals, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the account or disclosure to which it relates.

Clinical Trial Accrual

Description of the Matter

As discussed in Note 2 in the consolidated financial statements, the Company enters into contracts with clinical research organizations (CROs) to conduct clinical services on their behalf. Judgments and estimates are required to determine the amounts accrued for estimated ongoing research and development costs. The Company analyzes the progress of the studies or clinical trials, including the phase or completion of activities, invoices received and contracted costs.

Auditing the Company's accrual for clinical trial costs is complex since the information necessary to estimate the accruals is accumulated from the CROs and the Company's assessment of that information is subject to variability and uncertainty. In addition, in certain circumstances, the determination of the nature and amounts of services that have been received during the reporting period requires judgment because the timing and pattern of vendor invoicing does not correspond to the level of services provided, and there may be delays in invoicing from clinical study sites and other vendors.

How We Addressed the Matter in Our Audit

To test the clinical trial accrual, our audit procedures included, among others, reading a sample of the Company's agreement contracts with the CROs to understand key financial and contractual terms and testing the accuracy and completeness of the underlying data used in the accrual computations. We also evaluated management's estimates of the vendor's progress for a sample of clinical trials by inquiring of the Company's operations personnel overseeing the clinical trials and obtaining information directly from third party vendors regarding their estimate of costs that have been incurred through December 31, 2022. We analyzed the data underlying the accrual balance to evaluate the impact of reasonable changes in the data on the recorded amount of the clinical trial accrual. To evaluate the completeness of the accruals, we also examined subsequent invoices from the service providers and cash disbursements to the service providers, to the extent such invoices were received, or payments were made prior to the date that the consolidated financial statements were issued.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2020.

Iselin, New Jersey
March 9, 2023

Olema Pharmaceuticals, Inc.

Consolidated Balance Sheets

(Amounts in thousands, except for share amounts)

	<u>December 31,</u> <u>2022</u>	<u>December 31,</u> <u>2021</u>
Assets		
Current assets:		
Cash and cash equivalents	\$ 23,702	\$ 13,812
Marketable securities	180,719	273,438
Prepaid expenses and other current assets	4,478	3,435
Total current assets	<u>208,899</u>	<u>290,685</u>
Property and equipment, net	1,480	1,474
Operating lease right-of-use assets	2,495	3,246
Other assets	2,771	540
Total assets	<u>\$ 215,645</u>	<u>\$ 295,945</u>
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	\$ 374	\$ 23
Operating lease liabilities, current	1,015	931
Other current liabilities	15,160	8,065
Total current liabilities	<u>16,549</u>	<u>9,019</u>
Operating lease liabilities, net of current portion	1,550	2,358
Total liabilities	<u>18,099</u>	<u>11,377</u>
Commitments and contingencies (Note 12)		
Stockholders' equity:		
Preferred stock, \$0.0001 par value; 10,000,000 shares authorized as of December 31, 2022 and December 31, 2021; no shares issued and outstanding as of December 31, 2022 and December 31, 2021.	—	—
Common stock, \$0.0001 par value; 490,000,000 shares authorized as of December 31, 2022 and December 31, 2021; 40,601,648 and 40,337,046 shares issued as of December 31, 2022 and December 31, 2021, respectively; 40,287,097 and 39,797,263 shares outstanding as of December 31, 2022 and December 31, 2021, respectively.	3	3
Additional paid-in capital	408,333	388,904
Accumulated other comprehensive loss	(1,813)	(149)
Accumulated deficit	<u>(208,977)</u>	<u>(104,190)</u>
Total stockholders' equity	<u>197,546</u>	<u>284,568</u>
Total liabilities and stockholders' equity	<u>\$ 215,645</u>	<u>\$ 295,945</u>

See accompanying notes to the consolidated financial statements.

Olema Pharmaceuticals, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(Amounts in thousands, except for share and per share amounts)

	Years Ended December 31,	
	2022	2021
Operating expenses:		
Research and development	\$ 82,274	\$ 51,100
General and administrative	24,714	20,391
Total operating expenses	<u>106,988</u>	<u>71,491</u>
Loss from operations	(106,988)	(71,491)
Other income (expense):		
Interest income	2,228	442
Other expense	(27)	(47)
Total other income	<u>2,201</u>	<u>395</u>
Net loss	<u>\$ (104,787)</u>	<u>\$ (71,096)</u>
Net loss per share, basic and diluted	<u>\$ (2.62)</u>	<u>\$ (1.80)</u>
Weighted average shares used to compute net loss per share, basic and diluted	<u>39,995,460</u>	<u>39,524,272</u>

	Years Ended December 31,	
	2022	2021
Net loss	\$ (104,787)	\$ (71,096)
Other comprehensive loss:		
Net unrealized loss on marketable securities	(1,664)	(149)
Total comprehensive loss	<u>\$ (106,451)</u>	<u>\$ (71,245)</u>

See accompanying notes to the consolidated financial statements.

Olema Pharmaceuticals, Inc.

Consolidated Statements of Stockholders' Equity

(Amounts in thousands, except for share amounts)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balances at December 31, 2020	39,308,238	\$ 3	\$ 371,228	—	(33,094)	\$ 338,137
Vesting of early exercised stock options	79,608	—	372	—	—	372
Vesting of restricted stock awards	242,109	—	—	—	—	—
Exercise of stock options	126,937	—	670	—	—	670
Issuance of shares under the ESPP plan	40,371	—	721	—	—	721
Stock-based compensation expense	—	—	15,680	—	—	15,680
ESPP expense	—	—	233	—	—	233
Net unrealized loss on marketable securities	—	—	—	(149)	—	(149)
Net loss	—	—	—	—	(71,096)	(71,096)
Balances at December 31, 2021	39,797,263	\$ 3	\$ 388,904	\$ (149)	(104,190)	\$ 284,568
Vesting of early exercised stock options	27,958	—	124	—	—	124
Vesting of restricted stock awards	197,274	—	—	—	—	—
Exercise of stock options	87,490	—	146	—	—	146
Issuance of shares under the ESPP plan	177,112	—	330	—	—	330
Stock-based compensation expense	—	—	18,453	—	—	18,453
ESPP expense	—	—	376	—	—	376
Net unrealized loss on marketable securities	—	—	—	(1,664)	—	(1,664)
Net loss	—	—	—	—	(104,787)	(104,787)
Balances at December 31, 2022	40,287,097	\$ 3	\$ 408,333	\$ (1,813)	(208,977)	\$ 197,546

See accompanying notes to the consolidated financial statements.

Olema Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows
(Amounts in thousands)

	Years Ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	\$ (104,787)	\$ (71,096)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization expense	357	163
Non-cash lease expense	1,301	1,224
Premium amortization and discount accretion on marketable securities, net	(787)	276
Stock-based compensation expense, including ESPP expense	18,829	15,913
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(1,959)	(40)
Other assets	(1,114)	(30)
Accounts payable	351	(683)
Other current liabilities	7,018	4,571
Operating lease liabilities	(1,274)	(988)
Net cash used in operating activities	<u>(82,065)</u>	<u>(50,690)</u>
Cash flows from investing activities:		
Purchase of equipment	(363)	(1,575)
Maturities of marketable securities	305,502	213,104
Purchases of marketable securities	(213,660)	(486,967)
Net cash provided by (used in) investing activities	<u>91,479</u>	<u>(275,438)</u>
Cash flows from financing activities:		
Proceeds from exercise of stock options	146	670
Proceeds from issuance of common stock under the ESPP plan	330	721
Net cash provided by financing activities	<u>476</u>	<u>1,391</u>
Net increase (decrease) in cash and cash equivalents	<u>9,890</u>	<u>(324,737)</u>
Cash and cash equivalents at beginning of period	13,812	338,549
Cash and cash equivalents at end of period	<u>\$ 23,702</u>	<u>\$ 13,812</u>
Supplemental disclosure of non-cash investing and financing activities:		
Reclassification of prepaid expenses and other current liabilities into other assets	\$ 1,117	\$ —
Vesting of early exercised stock options	\$ 124	\$ 372

See accompanying notes to the consolidated financial statements.

Olema Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

1. Nature of the Business and Basis of Presentation

Olema Pharmaceuticals, Inc. (“Olema” or the “Company”) is a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of next-generation targeted therapies for women’s cancers. The Company is initially focused on developing therapies for the treatment of breast cancer. The Company’s wholly owned, lead product candidate, OP-1250, is a novel oral therapy with combined activity as both a complete estrogen receptor (“ER”) antagonist (“CERAN”) and a selective ER degrader (“SERD”). It is currently being evaluated as a single agent in an ongoing Phase 1/2 clinical study, and in Phase 1b/2 combination with palbociclib, ribociclib, and alpelisib, in patients with recurrent, locally advanced or metastatic estrogen receptor-positive (“ER+”), human epidermal growth factor receptor 2-negative (“HER2-”) breast cancer.

The Company is located in San Francisco, California and was incorporated in Delaware on August 7, 2006 under the legal name of CombiThera, Inc. and on March 25, 2009 was renamed Olema Pharmaceuticals, Inc. The Company’s principal operations are based in San Francisco, California, and has operations in Cambridge, Massachusetts. Olema Oncology Australia Pty Ltd was incorporated on January 6, 2021 and is a wholly-owned subsidiary of the Company (collectively with Olema Pharmaceuticals, Inc. referred to as “Olema” or the “Company” herein). It operates in one business segment and therefore has only one reportable segment. The Company is subject to risks and uncertainties common to early-stage companies in the biopharmaceutical industry, including, but not limited to, successful discovery and development of its product candidates, development by competitors of new technological innovations, dependence on key personnel, the ability to attract and retain qualified employees, protection of proprietary technology, compliance with governmental regulations, the impact of COVID-19 and other geopolitical and macroeconomic events, such as the COVID-19 pandemic and the ongoing conflict between Ukraine and Russia and related sanctions, the ability to secure additional capital to fund operations and commercial success of its product candidates. OP-1250 and any future product candidates the Company may develop will require extensive nonclinical and clinical testing and regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel, and infrastructure and extensive compliance-reporting capabilities. Even if the Company’s product development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Liquidity

The Company had \$204.4 million of cash, cash equivalents and marketable securities at December 31, 2022, which management believes is sufficient to fund its operating expenses and capital expenditure requirements into 2025.

Impact of COVID-19 and Other Geopolitical and Macroeconomic Events

The extent of the impact of the COVID-19 pandemic on the Company’s business, operations and development timelines and plans remains uncertain, and will depend on certain developments, including the duration of the outbreak and its impact on the Company’s development activities, planned clinical trial enrollment, future trial sites, contract research organizations (“CROs”), third-party manufacturers, and other third parties with whom the Company does business, as well as its impact on regulatory authorities and the Company’s key scientific and management personnel. During 2021 and 2022, although the Company modified its operations and practices due to the COVID-19 pandemic and to comply with federal, state and local requirements, its business, operations and development timelines were not material adversely affected. In October 2021, the Company re-opened its offices to administrative employees, however due to the resurgence of cases relating to the spread of the Delta and Omicron variants, the Company continued to limit access to its offices. In March 2022, the Company fully re-opened its offices to all employees and continues to comply with protocols implemented by

respective health authorities. As a result of the COVID-19 pandemic, we experienced some delays in setting up our current Phase 1/2 clinical study and in clinical site initiation, including delays in recruiting clinical site investigators and clinical site staff. We also experienced subject enrollment timeline delays in a Phase 1b clinical study of OP-1250 in combination with another CDK4/6 inhibitor and with a PI3K α inhibitor. We may experience these or other continuing impacts of the COVID-19 pandemic in the future. The Company continues to monitor developments related to COVID-19 and may close its offices again in the future. The extent to which the COVID-19 pandemic may affect the Company's business, operations and development timelines and plans in the future, including the resulting impact on its expenditures and capital needs, remains uncertain.

In addition to the ongoing COVID-19 pandemic, global economic and business activities continue to face widespread macroeconomic uncertainties, including labor shortages, inflation and monetary supply shifts, recession risks and potential disruptions from the Russia-Ukraine conflict, which has resulted in volatility in the U.S. and global financial markets and which has led to, and may continue to lead to, additional disruptions to trade, commerce, pricing stability, credit availability and supply chain continuity globally. The extent of the impact of these factors on the Company's operational and financial performance, including its ability to execute its business strategies and initiatives in the expected time frame, will depend on future developments, which are uncertain and cannot be predicted. Any continued or renewed disruption resulting from these factors could negatively impact the Company's business. The Company continues to monitor the impact of these macroeconomic factors on its results of operations, financial condition and cash flows.

2. Summary of Significant Accounting Policies

Basis of Presentation and Consolidation

The accompanying consolidated financial statements have been prepared in accordance with generally accepted accounting principles in the United States ("GAAP") and applicable rules and regulations of the Securities and Exchange Commission (the "SEC") regarding financial reporting, and the instructions to Form 10-K and Article 10 of Regulation S-X. These consolidated financial statements include the accounts of Olema Pharmaceuticals, Inc. and its wholly owned subsidiary, Olema Oncology Australia Pty Ltd. All intercompany balances and transactions have been eliminated upon consolidation.

Use of Estimates

The accompanying consolidated financial statements are prepared in accordance with GAAP. The preparation of the consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities at the date of the consolidated financial statements and reported amounts of expenses during the reporting period. Significant areas that require management's estimates include accruals of research and development expenses, including accrual of research contract costs, stock-based compensation assumptions, including the fair value of common stock. On an ongoing basis, the Company evaluates its estimates and judgments, which are based on historical and anticipated results and trends and on various other assumptions that management believes to be reasonable under the circumstances. Actual results could differ from those estimates.

Cash and Cash Equivalents

Cash and cash equivalents are defined as short-term, highly liquid investments with original maturities of 90 days or less at the date of purchase. Cash deposits are all in reputable financial institutions in the United States as of December 31, 2022 and 2021. Cash and cash equivalents consisted of cash on deposit with U.S. banks, including the Company's bank account for its Australia subsidiary, denominated in U.S. dollars and Australian dollars and investments in interest bearing money market funds.

Marketable Securities

All marketable securities have been classified as “available-for-sale” and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its investments at the time of purchase and reevaluates such designation as of each balance sheet date. Unrealized gains and losses are excluded from net loss and are reported as a component of comprehensive loss. Realized gains and losses and declines in fair value judged to be other than temporary, if any, on available-for-sale securities are included in interest income. The cost of securities sold is based on the specific-identification method. Interest earned on marketable securities is included in interest income.

The Company periodically assesses its available-for-sale marketable securities for other-than-temporary impairment. For debt securities in an unrealized loss position, the Company first considers its intent to sell, or whether it is more likely than not that the Company will be required to sell the debt securities before recovery of their amortized cost basis. If either of these criteria are met, the amortized cost basis of such debt securities is written down to fair value through other expense.

For debt securities in an unrealized loss position that do not meet the aforementioned criteria, the Company assesses whether the decline in the fair value of such debt securities has resulted from credit losses or other factors. The Company considers the extent to which fair value is less than amortized cost, any changes to the rating of the security by a rating agency, and any adverse conditions specifically related to the securities, among other factors. If this assessment indicates that a credit loss may exist, the Company then compares the present value of cash flows expected to be collected from such securities to their amortized cost basis. If the present value of cash flows expected to be collected is less than the amortized cost basis, a credit loss exists and an allowance for credit losses is recorded through other expense, limited by the amount that the fair value is less than the amortized cost basis. Any additional impairment not recorded through an allowance for credit losses is recognized in other comprehensive loss. The Company has not recorded any impairments for its marketable securities.

Concentration of Credit Risk and Other Risks and Uncertainties

Financial instruments that potentially subject the Company to concentration of credit risk consist of cash, cash equivalents, and marketable securities. The Company invests in a variety of financial instruments and, by its policy, limits these financial instruments to high credit quality securities issued by the U.S. government, U.S. government-sponsored agencies and highly rated banks and corporations, subject to certain concentration limits. The Company’s cash, cash equivalents, and marketable securities are held by financial institutions in the United States that management believes are of high credit quality. Amounts on deposit with individual banking institutions may at times exceed the limits insured by the Federal Deposit Insurance Corporation (“FDIC”); however, the Company has not experienced any losses on such deposits.

The Company’s future results of operations involve a number of other risks and uncertainties. Factors that could affect the Company’s future operating results and cause actual results to vary materially from expectations include, but are not limited to, uncertainty of results of clinical trials and reaching milestones, uncertainty of regulatory approval of the Company’s current and potential future product candidates, uncertainty of market acceptance of the Company’s product candidates, competition from substitute products and larger companies, securing and protecting proprietary technology, strategic relationships and dependence on key individuals or sole-source suppliers.

The Company’s product candidates require approvals from the U.S. Food and Drug Administration (“FDA”) and comparable foreign regulatory agencies prior to commercial sales in their respective jurisdictions. There can be no assurance that any product candidates will receive the necessary approvals. If the Company were denied approval, approval was delayed or the Company was unable to maintain approval for any product candidate, it could have a materially adverse impact on the Company.

Leases

In February 2016, the Financial Accounting Standards Board (“FASB”) issued new lease accounting guidance in Accounting Standard Update (“ASU”) 2016-02, *Leases*, and in July 2018 issued ASU 2018-10, *Codification Improvements to Topic 842, Leases*, and ASU 2018-11, *Leases (Topic 842): Targeted Improvements* (the foregoing ASUs collectively referred to as “Topic 842”). Under the new guidance, lessees are required to recognize for all leases (with the exception of short-term leases) at the commencement date: (1) a lease liability, which is a lessee’s obligation to make lease payments arising from a lease, measured on a discounted basis; and (2) a right-of-use (“ROU”) asset, which is an asset that represents the lessee’s right to use, or control the use of, a specified asset for the lease term. Leases will be classified as finance or operating, with classification affecting the pattern and classification of expense recognition in the consolidated statements of operations and comprehensive loss.

At the inception of an arrangement, the Company determines if an arrangement is, or contains, a lease based on the facts and circumstances present in that arrangement. Lease classification, recognition, and measurement are then determined at the lease commencement date. For arrangements that contain a lease, the Company (i) identifies lease and non-lease components, (ii) determines the consideration in the contract, (iii) determines whether the lease is an operating or finance lease; and (iv) recognizes lease ROU assets and liabilities. Lease liabilities and their corresponding ROU assets are recorded based on the present value of future lease payments over the expected lease term. The interest rate implicit in lease contracts is typically not readily determinable and as such, the Company uses the incremental borrowing rate based on the information available at the lease commencement date, which represents an internally developed rate that would be incurred to borrow, on a collateralized basis, over a similar term, an amount equal to the lease payments in a similar economic environment.

Most leases include options to renew and, or terminate the lease, which can impact the lease term. The exercise of these options is at the Company’s discretion. The Company’s lease terms may include options to extend or terminate the lease when it is reasonably certain that the Company will exercise such options. For any lease modification, the Company reassesses the lease classification, remeasures the related lease liability using an updated discount rate that reflects the modified lease term, and adjusts the related ROU asset under the lease modification guidance under Topic 842.

The Company has operating leases for its research and development and office facilities. Fixed lease payments on operating leases are recognized over the expected term of the lease on a straight-line basis. Variable lease expenses that are not considered fixed are recognized as incurred. Fixed and variable lease expense on operating leases is recognized within operating expenses within our consolidated statements of operations and comprehensive loss.

The Company elected to not apply the recognition requirements of Topic 842 to short-term leases with terms of 12 months or less. Additional information and disclosures required by Topic 842 are contained in Note 11 “Lease”.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred to discover, research and develop product candidates. These costs are recorded within research and development expenses in the consolidated statements of operations and include personnel expenses, stock-based compensation expenses, allocated general and administrative expenses, and external costs including fees paid to consultants and CROs and contract manufacturing organizations (“CMOs”), in connection with nonclinical studies and clinical trials, and other related clinical trial fees, such as for investigator fees, patient screening, laboratory work, clinical trial database management, clinical trial material management and statistical compilation and analysis. Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are recorded as prepaid expenses and other current

assets. Such amounts are recognized as an expense as the goods are delivered or the related services are performed.

Costs incurred in obtaining technology licenses that do not meet the definition of a business are charged immediately to research and development expense if the technology licensed has not reached technological feasibility and has no alternative future uses.

Reimbursements of certain costs associated with research activities performed under the agreement with Novartis Institutes for BioMedical Research, Inc. (“Novartis”) are recorded as a reduction of research and development expenses, as described in Note 12, Commitments and Contingencies – *Clinical Collaboration and Supply Agreement*.

Research Contract Costs and Accruals

The Company has from time to time entered into various research and development and other agreements with commercial firms, researchers, universities and others for provisions of goods and services. These agreements are generally cancelable, and the related costs are recorded as research and development expenses as incurred.

The Company records accruals for estimated ongoing research and development costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the projects, studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ materially from the Company’s estimates. The Company’s historical accrual estimates have not been materially different from the actual costs.

Property and Equipment

Property and equipment are stated at cost, net of accumulated depreciation. Depreciation is computed using the straight-line method over the estimated useful lives. The useful lives of equipment are as follows:

	<u>Estimated Useful Lives</u>
Lab equipment	5 – 7 years
Computer equipment	5 years

When assets are sold or retired, the cost and related accumulated depreciation are removed from the balance sheets, with any resulting gain or loss recorded in operating expenses in the statements of operations and comprehensive loss. Costs of repairs and maintenance are expensed as incurred.

Income Taxes

Income taxes are computed using the asset and liability approach that requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the Company’s consolidated financial statements. In estimating future tax consequences, the Company considers all expected future events other than enactment of changes in tax laws or rates. A valuation allowance is recorded, if necessary, to reduce net deferred tax assets to their realizable values if management does not believe it is more likely than not that the net deferred tax assets will be realized. As of December 31, 2022 and 2021, the Company has recorded full valuation allowance against its net deferred tax assets.

The Company had no unrecognized tax benefits for the years ended December 31, 2022 and 2021, respectively. The Company may be subject to U.S. Federal, state, and local tax examinations by tax authorities for years before 2022, which may include adjustments to carry-forward attributes (see Note 9, “Income Taxes”).

The Company's policy is to recognize interest and penalties related to uncertain tax positions in the provision for income taxes. As of December 31, 2022 and 2021, the Company had no accrued interest or penalties related to uncertain tax positions.

Comprehensive Loss

Comprehensive loss includes net loss and other comprehensive loss for each period presented. Other comprehensive loss represents net unrealized loss on marketable securities.

Stock-Based Compensation

Stock-based compensation cost, including grants of stock options and restricted stock awards issued under the Company's equity incentive plans and ESPP, is measured at the grant date based on the estimated fair value of the award and is recognized as an expense on a straight-line basis over the requisite service period, which is generally the vesting period. Stock-based compensation cost for performance-based restricted stock unit awards issued under the Company's equity incentive plan is measured at the grant date based on the estimated fair value of the award, which is based on the closing stock price on the grant date, and is recognized as an expense when the Company determines that it is probable that the performance goals will be achieved, which the Company assess on a quarterly basis. The Company recognizes stock compensation in accordance with ASC 718, Compensation — Stock Compensation ("ASC 718"). The Company's determination of the fair value of stock options with time-based vesting on the date of grant utilizes the Black-Scholes option-pricing model. The Company estimates volatility using stock prices of peer companies and its historical data, risk-free rates using the implied yield currently available on U.S. Treasury zero-coupon issues with a remaining term equal to the expected term, and dividend yield using the Company's expectations and historical data. The Company uses the simplified method to calculate the expected term of employee stock option grants. Under the simplified method, the expected term is estimated to be the mid-point between the vesting date and the contractual term of the option. For awards with graded vesting, in which specified tranches of the options vest on different dates, the Company uses a single weighted average expected life to value the entire award, which is equal to the average of the weighted average vesting period of the award and the contractual term of the award. Equity instruments issued to nonemployees are recorded at their fair value on the grant date and without subsequent remeasurement. The amount of stock-based compensation expense recognized during a period is based on the value of the portion of the awards that are ultimately expected to vest, including awards with graded vesting. As part of the requirements of ASC 718, the Company has elected to account for forfeitures of stock option grants as they occur.

Foreign Currency Transactions

The functional currency of Olema Oncology Australia Pty Ltd, the Company's wholly-owned subsidiary, is the U.S. dollar. Accordingly, all monetary assets and liabilities of the subsidiary are remeasured into U.S. dollars at the current period-end exchange rates and non-monetary assets are remeasured using historical exchange rates. Income and expense elements are remeasured to U.S. dollars using the average exchange rates in effect during the period. Remeasurement gains and losses are recorded as other income (expense) on the consolidated statements of operations.

The Company is subject to foreign currency risk with respect to its clinical and manufacturing contracts denominated in currencies other than the U.S. dollar, predominantly the Australian dollar and the Euro. Payments on contracts denominated in foreign currencies are made at the spot rate on the day of payment. Changes in the exchange rate between billing dates and payment dates are recorded within other income (expense) on the consolidated statements of operations.

Net Loss Per Common Share

Basic net loss per common share is computed by dividing the net loss per common share by the weighted average number of common shares outstanding for the period without consideration of common stock

equivalents. Diluted net loss per common share is computed by adjusting net loss to reallocate undistributed earnings based on the potential impact of dilutive securities, and by dividing the diluted net loss by the weighted average number of common shares outstanding for the period, including potential dilutive common shares. For purpose of this calculation, outstanding stock options, including unvested early exercised options, unvested restricted stock awards, unvested performance-based restricted stock unit awards, contingently issuable common stock related to the 2020 Employee Stock Purchase Plan (the “ESPP”) are considered potential dilutive common shares. Since the Company was in a loss position for all periods presented, basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all potential common shares outstanding would have been anti-dilutive.

Recent Accounting Pronouncements

There were no new accounting pronouncements that were relevant to the Company as of and for the year ended December 31, 2022.

3. Fair Value Measurement

The Company assesses the fair value of financial instruments based on the provisions of ASC 820, Fair Value Measurements. ASC 820 defines fair value as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. ASC 820 also establishes a fair value hierarchy which requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value. The standard describes three levels of inputs that may be used to measure fair value:

- Level 1 — Inputs are unadjusted quoted prices in active markets for identical assets or liabilities accessible to the reporting entity at the measurement date.
- Level 2 — Inputs other than quoted prices included in Level 1 that are observable for the asset or liability, such as quoted prices for similar assets or liabilities, quoted prices in markets that are not active, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.
- Level 3 — Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

(in thousands)	December 31, 2022			
	Level 1	Level 2	Level 3	Total
Financial Assets				
Cash	\$ 7,273	\$ —	\$ —	\$ 7,273
Money market funds	16,549	—	—	16,549
Commercial paper	—	83,188	—	83,188
U.S. government treasury bills	77,025	—	—	77,025
Government-sponsored enterprise securities	—	20,507	—	20,507
Total	\$ 100,847	\$ 103,695	\$ —	\$ 204,542

(in thousands)	December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Financial Assets				
Cash and cash equivalents	\$ 23,822	\$ —	\$ —	\$ 23,822
Short-term marketable securities (<12 months to maturity).	182,533	17	(1,830)	180,720
Long-term marketable securities (>12 months to maturity).	—	—	—	—
Total	\$ 206,355	\$ 17	\$ (1,830)	\$ 204,542

The Company considers its marketable securities with maturities beyond one year as current assets, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company considers its investment portfolio of marketable securities to be available-for-sale.

The Company periodically reviews its available-for-sale marketable securities for other-than-temporary impairment. The Company considers factors such as the duration, severity and the reason for the decline in value, the potential recovery period and its intent to sell. For debt securities, the Company also considers whether (i) it is more likely than not that the Company will be required to sell the debt securities before recovery of their amortized cost basis, and (ii) the amortized cost basis cannot be recovered as a result of credit losses.

There were five marketable securities that have been in a consecutive loss position for more than 12 months as of December 31, 2022. They had \$0.3 million unrealized loss with a fair value of \$12.7 million as of December 31, 2022. The Company does not believe that the total unrealized losses of \$1.8 million as of December 31, 2022 are credit related but are rather a reflection of current market yields and/or current marketplace bid/ask spreads. During the years ended December 31, 2022 and 2021, respectively, the Company did not recognize any other-than-temporary impairment loss. As of December 31, 2022, there was no allowance for losses on available-for-sale debt securities attributable to credit risk.

As of December 31, 2022, all of the Company's cash and cash equivalents consisted of cash on deposit with U.S. banks denominated in U. S. dollars and Australian dollars.

4. Property and Equipment, net

Property and equipment, net consisted of the following (in thousands):

	December 31, 2022	December 31, 2021
Lab equipment	\$ 2,002	\$ 1,639
Computer equipment	59	59
Property and equipment, gross.	2,061	1,698
Less: Accumulated depreciation	(581)	(224)
Property and equipment, net.	\$ 1,480	\$ 1,474

5. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following (in thousands):

	<u>December 31,</u> <u>2022</u>	<u>December 31,</u> <u>2021</u>
Prepaid insurance	\$ 1,738	\$ 1,766
Reimbursable research and development costs from a collaboration partner . . .	1,387	—
Prepaid clinical trial costs	506	916
Prepaid subscriptions and licenses	399	291
Interest receivable	319	130
Prepaid research contracts	12	239
Other	117	93
Total	\$ 4,478	\$ 3,435

6. Other Current Liabilities

Other current liabilities consisted of the following (in thousands):

	<u>December 31,</u> <u>2022</u>	<u>December 31,</u> <u>2021</u>
Accrued research and development related costs	\$ 9,105	\$ 2,645
Accrued employee bonuses	4,518	3,752
Accrued professional fees	1,091	1,011
Accrued payroll related costs	296	191
Early exercise of unvested stock options	82	206
Accrued taxes	67	88
Other	1	172
Total	\$ 15,160	\$ 8,065

7. Common Stock

As of each of the balance sheet dates below, the Company had reserved shares of common stock for issuance in connection with the following:

	<u>December 31,</u> <u>2022</u>	<u>December 31,</u> <u>2021</u>
Options outstanding under the 2014 Stock Plan ⁽¹⁾⁽²⁾	2,332,441	2,447,889
Options outstanding under the 2020 Equity Incentive Plan	5,332,617	3,320,139
Options outstanding under the 2022 Inducement Plan	719,800	—
Shares available for future grant under the 2020 Equity Incentive Plan and the 2022 Inducement Plan	1,392,584	818,010
Available for the 2020 Employee Stock Purchase Plan	1,018,000	791,742
Unvested performance-based restricted stock unit awards outstanding under the 2020 Equity Incentive Plan	710,000	—
Unvested restricted stock awards outstanding under the 2014 Stock Plan	295,911	493,185
	<u>11,801,353</u>	<u>7,870,965</u>

(1) Balance as of December 31, 2022 includes 18,640 unvested early exercised stock options (see Note 8, "Stock-Based Compensation").

(2) Balance as of December 31, 2021 includes 46,598 unvested early exercised stock options (see Note 8, "Stock-Based Compensation").

8. Stock-Based Compensation

In 2014, the Company's Board of Directors and stockholders approved and adopted the 2014 Stock Plan (the "2014 Plan"). The 2014 Plan permitted the grant of options and restricted stock awards (including restricted stock purchase rights and restricted stock bonus awards). The 2014 Plan was terminated on the date the 2020 Equity Incentive Plan (the "2020 Plan"), which is described below, became effective, and no additional awards will be made pursuant to the 2014 Plan. However, any outstanding awards granted under the 2014 Plan will remain outstanding, subject to the terms of the 2014 Plan award agreements, until such outstanding options are exercised or until any awards terminate or expire by their terms.

In 2020, the Company's Board of Directors and stockholders approved and adopted the 2020 Equity Incentive Plan (the "2020 Plan"). The 2020 Plan permits the grant of options, restricted stock awards, stock appreciation rights, restricted stock unit awards, performance awards, and other awards. The maximum number of shares of common stock that may be issued under the 2020 Plan will not exceed 6,494,510 shares of the Company's common stock, which is the sum of (i) 2,152,080 new shares, plus (ii) an additional number of shares not to exceed 4,342,430 shares, consisting of any shares of the Company's common stock subject to outstanding stock options or other stock awards granted under the Company's 2014 Plan that, on or after the 2020 Plan becomes effective, terminate or expire prior to exercise or settlement; are not issued because the award is settled in cash; are forfeited because of the failure to vest; or are reacquired or withheld (or not issued) to satisfy a tax withholding obligation or the purchase or exercise price. In addition, the number of shares of the Company's common stock reserved for issuance under the 2020 Plan automatically increases on January 1 of each year for a period of ten years, beginning on January 1, 2021 and continuing through January 1, 2030, in an amount equal to the lesser of (1) 5% of the total number of shares of the Company's common stock outstanding on December 31 of the immediately preceding year, or (2) a lesser number of shares determined by the Company's board of directors no later than December 31 of the immediately preceding year.

In 2022, the Company's Board of Directors approved and adopted the 2022 Inducement Plan (the "2022 Inducement Plan"). Under the 2022 Inducement Plan, initially 2,000,000 shares of common stock were reserved for issuance. The 2022 Inducement Plan permits the grant of options, restricted stock awards, stock appreciation rights, restricted stock unit awards, performance awards, and other awards.

The exercise price for each option and stock appreciation right shall be established at the discretion of the Board, provided that the exercise price of a stock option will not be less than 100% of the fair market value of the Company's common stock on the date of grant. Specific vesting for stock options and stock appreciation rights is service related and determined in each award agreement, where stock options and stock appreciation rights are fully vested at the grant date or follow a graded vesting schedule. Stock options and stock appreciation rights granted under the Plan generally expire ten years after the date of grant.

Stock Option Valuation

The fair value of stock option grants is estimated using the Black-Scholes option-pricing model. The Company lacks company-specific historical and implied volatility information. Therefore, it estimated its expected stock volatility based on the historical volatility of a publicly traded set of peer companies in addition to its own historical volatility. For options with service-based vesting conditions, the expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The expected term of stock options granted to nonemployees is equal to the contractual term of the option award. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is 0% since the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

The assumptions that the Company used to determine the estimated grant-date fair value of stock options granted to employees and directors under the 2020 Plan and the 2022 Inducement Plan were as follows, presented as a weighted average:

	December 31, 2022	December 31, 2021
Risk-free interest rate	1.99%	0.95%
Expected term (in years)	6.03	5.97
Expected volatility	79.71%	77.55%
Expected dividend yield	—	—

Stock Option Activity

The following table summarizes the stock option activity under the 2014 Plan, the 2020 Plan and the 2022 Inducement Plan:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2021	5,768,028	\$ 15.99	8.82	\$ 11,365
Granted	3,293,640	5.53	—	—
Exercised(1)	(115,448)	3.06	—	—
Forfeited	(561,362)	23.64	—	—
Outstanding as of December 31, 2022(2)	8,384,858	\$ 8.59	8.30	\$ 262
Options vested and exercisable as of				
December 31, 2022	3,270,694	\$ 10.21	7.79	\$ 215
Options expected to vest as of December 31, 2022 . . .	5,114,164	\$ 7.56	8.63	\$ 47

(1) Exercised amount includes vesting of early exercised options.

(2) Balance as of December 31, 2022 includes 18,640 unvested early exercised stock options.

The weighted-average grant-date fair value per share of options granted during the years ended December 31, 2022 and 2021 was \$3.83 and \$21.87, respectively. For the years ended December 31, 2022 and 2021, there were 1,670,701 and 1,286,729 shares vested, respectively. The weighted-average grant date fair value per share of options vested during the years ended December 31, 2022 and 2021 was \$6.76 and \$7.48, respectively. The total fair value of options vested during the years ended December 31, 2022 and 2021 was \$11.3 million and \$10.9 million, respectively. The aggregate intrinsic value of options exercised during the years ended December 31, 2022 and 2021 was \$0.3 million and \$0.7 million, respectively.

As of December 31, 2022, the total unrecognized compensation expense related to unvested options was \$34.7 million, which the Company expects to recognize over an estimated weighted average period of 2.54 years.

Early Exercise of Stock Options

In September 2020, one employee and one non-employee paid \$0.6 million to early exercise 135,525 options with exercise prices ranging from \$4.406 per share to \$4.824 per share. As of December 31, 2022, 116,885 of such shares had vested with the remaining shares vesting over their respective terms. The terms of the 2014 Plan permit certain option holders to exercise options before their options are vested, subject to certain limitations. The early exercised options are subject to the same vesting provisions in the original stock option awards. Shares issued as a result of early exercise that have not vested are subject to repurchase by the Company upon termination of the purchaser's employment, at the price paid by the purchaser. Such shares

are not deemed to be outstanding for accounting purposes until they vest and are therefore excluded from shares outstanding and from basic and diluted net loss per share until the repurchase right lapses and the shares are no longer subject to the repurchase feature. A liability is recognized related to the cash proceeds of the unvested options and is reclassified into common stock and additional paid-in capital as the shares vest and the repurchase right lapses. Accordingly, the Company has recorded the unvested portion of the exercise proceeds of \$0.1 million in other current liabilities as of December 31, 2022.

Restricted Stock Awards

In June 2020, the Company granted to certain employees 789,095 shares of restricted common stock (the “RSAs”) under the 2014 Plan as consideration for services with a deemed value of \$2.40 per share, or \$1.9 million. The following table summarizes the restricted stock activity under the Plan during the year ended December 31, 2022:

	Number of Shares	Grant Date Fair Value
Unvested restricted stock as of December 31, 2021	493,185	\$ 2.40
Granted	—	
Vested	(197,274)	2.40
Forfeited	—	
Unvested restricted stock as of December 31, 2022	295,911	\$ 2.40

The total grant date fair value of the RSAs vested during the year ended December 31, 2022, was \$0.5 million. As of December 31, 2022, the total unrecognized compensation expense related to unvested RSAs was \$0.7 million, which the Company expects to recognize over an estimated weighted average period of 1.5 years.

Performance-Based Restricted Stock Unit Awards

In November 2022, the Company granted to certain employees 710,000 shares of performance-based restricted stock unit awards (the “PSUs”) under the 2020 Plan as consideration for services subject to performance conditions with a fair value based on the closing price of the underlying common stock on the date of grant. Pursuant to the terms of the PSUs, 65% of each PSU vests upon certification by the Compensation Committee of the Company of achieving a pre-determined performance goal by June 30, 2024, and 35% of each PSU vests upon certification by the Compensation Committee of the Company of achieving a pre-determined performance goal by June 30, 2024.

Expense recognition for PSUs commences when it is determined that attainment of the performance goal is probable or met. As of December 31, 2022, it was determined that the performance goals were not yet met, and therefore, the Company recorded zero stock-based compensation expense related to the PSUs for the year ended December 31, 2022.

2020 Employee Stock Purchase Plan (“2020 ESPP”)

In 2020, the Company’s board of directors and stockholders approved and adopted the 2020 ESPP. The 2020 ESPP permits eligible employees who elect to participate in an offering under the 2020 ESPP to have up to 15% of their eligible earnings withheld, subject to certain limitations, to purchase shares of common stock pursuant to the 2020 ESPP. The price of the common stock purchased under the 2020 ESPP is equal to the lesser of (i) 85% of the fair market value of a share of the Company’s common stock on the first day of an offering; or (ii) 85% of the fair market value of a share of the Company’s common stock on the date of purchase. Each offering period is not to exceed 27 months and will include one or more purchase periods (each a “Purchase Period”) as approved by the Company’s board of directors in the offering. The current offering period will consist of two (2) six-month purchase periods (each a “Purchase Period”) during which payroll deductions of the participants are accumulated under the 2020 ESPP. The last business day of each Purchase Period is referred to as the “Purchase Date.” A total of 430,416 shares of common stock were initially reserved for issuance pursuant to the 2020 ESPP.

The 2020 ESPP is a compensatory plan as defined by the authoritative guidance for stock-based compensation. The Company uses the Black-Scholes option-pricing model to estimate the fair value of stock offered under the 2020 ESPP. Stock-based compensation expense related to the 2020 ESPP was \$0.4 million and \$0.2 million for the years ended December 31, 2022 and 2021, respectively.

Stock-Based Compensation Expense

Stock-based compensation expense related to awards granted under the 2014 Plan, including the RSAs, the 2020 Plan, the 2022 Inducement Plan, and the 2020 ESPP was classified in the consolidated statements of operations and comprehensive loss as follows (in thousands):

	Years Ended December 31,	
	2022	2021
Research and development	\$ 12,462	\$ 9,346
General and administrative	6,367	6,567
Total	\$ 18,829	\$ 15,913

9. Income Taxes

The reconciliation of the Federal statutory income tax (provision) benefit to the Company's effective income tax provision is as follows (in thousands):

	Years Ended December 31,	
	2022	2021
Federal statutory income tax	\$ 21,927	\$ 14,930
State income taxes, net of federal tax benefit	6,684	25
Permanent differences in non-tax-deductible executive compensation	(1,952)	(1,092)
Permanent differences in foreign jurisdiction	(450)	—
Permanent differences others	(608)	(105)
Foreign research and development tax credit	624	—
Other deferred items	(308)	158
Rate changes	(28)	—
Valuation allowance	(25,890)	(13,916)
Net expense for income taxes	\$ (1)	\$ —

Deferred income taxes reflect the net tax effects of loss and credit carryforwards and temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The Company's deferred income tax assets and liabilities at December 31, 2022 and 2021 comprised the following (in thousands):

	As of December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	\$ 27,449	\$ 17,889
Capitalized research and development	14,992	—
Equity compensation	4,786	2,530
Other	541	959
Total deferred tax assets	<u>\$ 47,768</u>	<u>\$ 21,378</u>
Deferred tax liabilities:		
Fixed assets	\$ (341)	\$ (310)
Total deferred tax liabilities	(341)	(310)
Valuation allowance	(47,427)	(21,068)
Net deferred tax assets	<u>\$ —</u>	<u>\$ —</u>

In assessing the realization of deferred tax assets, management considers whether it is more likely than not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during the periods in which those temporary differences become deductible. Management considers the scheduled reversal of deferred tax liabilities, projected future taxable income and tax planning strategies in making this assessment. Based on the level of historical operating results and the uncertainty of the economic conditions, the Company has recorded a valuation allowance of \$47.4 million and \$21.1 million at December 31, 2022 and 2021, respectively. The change in the valuation allowance for the year end December 31, 2022 was an increase of \$26.4 million.

At December 31, 2022 and 2021, the Company had Federal net operating losses (NOLs) of approximately \$115.0 million and \$81.8 million, and state NOLs of \$47.5 million and \$10.4 million, respectively. As a result of the Tax Act, as modified by the CARES Act, for U.S. income tax purposes, NOLs generated in tax years beginning before January 1, 2018 can still be carried forward for up to 20 years, but net operating losses generated for tax years beginning after December 31, 2017 carryforward indefinitely and can be used to offset taxable income, but the deductibility of such Federal NOLs may be limited to 80% of current year taxable income for tax years beginning on or after December 31, 2022. Of the total Federal net operating loss of \$115.0 million, \$3.3 million will begin to expire in 2032 and \$111.7 million will not expire. The state NOL carryover of \$47.5 million will begin to expire in 2032.

Pursuant to Internal Revenue Code (IRC) Sections 382 and 383, annual use of the Company's net operating loss and research and development credit carryforwards may be limited in the event a cumulative change in ownership of more than 50% occurs within a three-year period. The Company has not completed an ownership change analysis pursuant to IRC Section 382. If ownership changes within the meaning of IRC Section 382 are identified as having occurred, the amount of remaining tax attribute carryforwards available to offset future taxable income and income tax expense in future years may be significantly restricted or eliminated. Further, the Company's deferred tax assets associated with such tax attributes could be significantly reduced upon realization of an ownership change within the meaning of IRC Section 382 that has occurred or may occur in the future. Any adjustment to the Company's tax attributes as a result of an ownership change will result in a corresponding decrease to the valuation allowance recorded against the Company's deferred tax assets.

The Company's valuation allowance increased during the years ended December 31, 2022 and 2021 due primarily to the generation of net operating losses, as follows (in thousands):

	Years Ended December 31,	
	2022	2021
Valuation allowance at beginning of year	\$ 21,068	\$ 7,231
Increase recorded to provision for income taxes	26,359	13,837
Valuation allowance at end of year	<u>\$ 47,427</u>	<u>\$ 21,068</u>

The Company has not incurred any material interest or penalties as of the current reporting date with respect to income tax matters. The Company is subject to U.S. Federal and state income taxes. The Federal and state income tax returns for tax years prior to 2022 may remain open to examination as carry-forward attributes generated prior may be adjusted upon examination.

10. Net Loss Per Common Share

Net Loss Per Common Share

Basic and diluted net loss per common share was calculated as follows (in thousands, except share and per share amounts):

	Years Ended December 31,	
	2022	2021
Numerator:		
Net loss	\$ (104,787)	\$ (71,096)
Denominator:		
Weighted average shares used to compute net loss per share, basic and diluted	39,995,460	39,524,272
Net loss per share, basic and diluted	\$ (2.62)	\$ (1.80)

The potentially dilutive shares that were excluded from the calculation of diluted net loss per share because their effect would have been anti-dilutive for the periods presented are as follows:

	Years Ended December 31,	
	2022	2021
Unvested restricted common stock	295,911	493,185
Unvested performance-based restricted stock units	710,000	—
Options to purchase common stock	8,384,858	5,768,028
Employee stock purchase plan contingently issuable	79,153	17,110
	9,469,922	6,278,323

Included in the potentially dilutive options to purchase common stock are 18,640 unvested stock options that were early exercised by an employee and a non-employee in September 2020 (see Note 8, “Stock-Based Compensation”). The Company determined the early exercises to be non-substantive as the shares were subject to repurchase rights. Accordingly, the Company has excluded these shares from the calculation of basic and diluted net loss per share for the years ended December 31, 2022 and 2021.

11. Lease

The Company leases certain of its facilities under non-cancellable operating leases expiring at various dates through 2026.

On June 1, 2013, the Company entered into a management services agreement with MandalMed, Inc. (“MandalMed”) (the “MandalMed Services Agreement”) to have access to and use a portion of approximately 5,762 square feet of space for the use of laboratory benches, lab equipment, office space, and administrative and facilities services. The Company subsequently entered into six amendments to extend the agreement term to November 2023. As part of the sixth amendment, the Company gained access to use additional space of approximately 2,130 square feet (the “Additional Space”) for a three year period commencing on December 1, 2020 and ending on November 30, 2023. According to the terms of the MandalMed Services Agreement, the Company paid a security deposit of less than \$0.1 million and is required to pay monthly rent and common area charges.

On August 27, 2020, the Company entered into a lease agreement with 512 2nd Street LLC to lease approximately 3,500 square feet of office space in San Francisco, California (the "Office Space Lease Agreement"). The Office Space Lease Agreement is for a period of two years commencing on September 1, 2020 and ending August 31, 2022. In April 2022, the Company extended the Office Space Lease Agreement up to August 31, 2023 and has one year renewal option to extend the term up to August 31, 2024. According to the terms of the Office Space Lease Agreement, the Company paid a \$0.1 million security deposit and is required to pay monthly rent and common area charges. The extension of the lease term was accounted for as a modification under Topic 842 and the Company recorded additional ROU asset and lease liability of \$0.3 million and \$0.3 million, respectively, in the consolidated financial statements.

On December 15, 2020, the Company entered into a lease agreement with Tennieh LLC to lease approximately 9,800 square feet of office space in San Francisco, California (the "Laboratory Lease Agreement"). The Laboratory Lease Agreement is for a period of five years commencing approximately February 1, 2021 and ending January 31, 2026. According to the terms of the Laboratory Lease Agreement, the Company paid a \$0.4 million security deposit and is required to pay monthly rent and common area charges.

The following table summarizes total lease expense during the years ended December 31, 2022 and 2021 (in thousands):

	Years Ended December 31,	
	2022	2021
Straight-line operating lease expense	\$ 1,301	\$ 1,224
Variable lease expense	248	64
Short-term lease expense	49	112
Total operating lease expense	\$ 1,598	\$ 1,400

The following table summarizes supplemental cash flow information during the year ended December 31, 2022 and 2021 (in thousands):

	Years Ended December 31,	
	2022	2021
Cash paid for amounts included measurement of lease liabilities:		
Operating cash flows from operating leases	\$ 1,274	\$ 988
ROU asset obtained in exchange for a new operating lease liability	297	3,152

The following table summarizes the Company's future minimum lease payments and reconciliation of lease liabilities as of December 31, 2022 (in thousands):

Years Ended December 31,	
2023	\$ 1,185
2024	799
2025	822
2026	69
2027	—
Thereafter	—
Total future minimum lease payments	2,875
Less: Interest	(310)
Total lease liabilities at present value	2,565
Lease liabilities, current	1,015
Lease liabilities, non-current	\$ 1,550

The following table summarizes lease term and discount rate as of December 31, 2022 and 2021:

	Years Ended December 31,	
	2022	2021
Weighted-average remaining lease term (years)	2.73	3.63
Weighted-average discount rate	8.70%	8.65%

12. Commitments and Contingencies

Clinical Collaboration and Supply Agreement

On July 22, 2020, the Company entered into a non-exclusive clinical collaboration and supply agreement with Novartis Institutes for BioMedical Research, Inc. (“Novartis”) (the “Novartis Agreement”). The collaboration is focused on the evaluation of the safety, tolerability and efficacy of OP-1250 in combination with Novartis’ proprietary CDK4/6 inhibitor Kisqali® (ribociclib) and/or Novartis’ proprietary PI3K α inhibitor Piqray® (alpelisib) (collectively the “Novartis Study Drugs”) as part of the Company’s planned Phase 1b clinical study of OP-1250 in patients with metastatic estrogen receptor-positive breast cancer. The Company will be responsible for the conduct of the clinical trials for the combined therapies in accordance with a mutually agreed development plan. As part of the collaboration, the parties granted to each other a non-exclusive, royalty- free license under certain of the parties’ respective background patent rights and other technology to use the parties’ respective study drugs in research and development, solely to the extent reasonably needed for the other party’s activities in the collaboration. All inventions and data developed in the performance of the clinical trials for the combined therapies (other than those specific to each component study drug), will be jointly owned by the parties.

The Company is responsible for manufacturing, packaging and labeling OP-1250, and for packaging and labeling all drugs used in the clinical trials for the combined therapies (other than the Novartis Study Drugs). Novartis is responsible for manufacturing and delivering to the Company the Novartis Study Drugs in such quantities as reasonably needed for the clinical trials for the combined therapies. In accordance with an agreed budget, subject to certain thresholds, Novartis will reimburse the Company for a majority of the direct outside costs that the Company incurs related to conducting the activities under the agreed development plan in conducting the clinical trials for the combined therapies.

The Novartis Agreement will terminate upon completion of all activities outlined in the development plan and the relevant protocols. Either party may terminate the Novartis Agreement for the uncured material breach or insolvency of the other party, if it reasonably deems it necessary in order to protect the safety, health or welfare of subjects enrolled in the clinical trials for the combined therapies due to the existence of a material safety issue, or in certain circumstances for an unresolved clinical hold with respect to either the Novartis Study Drugs or OP-1250. In addition, Novartis may terminate the Novartis Agreement if certain disputes between the parties are not resolved after following the applicable dispute resolution procedures, and the Company may terminate the Novartis Agreement in the event the Company terminates all clinical trials of the combined therapies other than due to a material safety issue or upon a clinical hold.

Costs associated with research activities performed under the agreement are included in research and development expenses in the accompanying consolidated financial statements, with any reimbursable costs from Novartis reflected as a reduction of such expenses. For the year ended December 31, 2022, costs reimbursable from Novartis were \$1.4 million. As of December 31, 2022, the receivable due from Novartis was \$1.4 million, which is recorded under prepaid expenses and other current assets in the accompanying consolidated financial statements. There was no such cost incurred as of and for the year ended December 31, 2021.

Clinical Trial Agreement

In November 2020, the Company entered into a non-exclusive clinical trial agreement with Pfizer Inc. (“Pfizer”) (the “Pfizer Agreement”), to evaluate the safety and tolerability of OP-1250 in combination with Pfizer’s proprietary CDK4/6 inhibitor IBRANCE® (palbociclib) in patients with recurrent, locally advanced or metastatic ER+, HER2- breast cancer in a clinical trial. Under the terms of the non-exclusive agreement, the Company will be responsible for conducting the clinical trial for the combined therapies and Pfizer is responsible for supplying IBRANCE® to the Company at no cost to the Company. As part of the collaboration, the parties granted to each other a non-exclusive, royalty- free license under certain of the parties’ respective patent rights in the combination of IBRANCE® and OP-1250 to use the parties’ respective study drugs in research and development, solely to the extent reasonably needed for the other party’s activities in the collaboration. All inventions and data developed in the performance of the clinical trials for the combined therapies (other than those specific to each component study drug), will be jointly owned by the parties.

The Company is responsible for manufacturing, packaging and labeling OP-1250, and for packaging and labeling all drugs used in the clinical trials for the combined therapies (other than IBRANCE® (palbociclib)). Pfizer is responsible for manufacturing and delivering to us IBRANCE® (palbociclib) in such quantities as reasonably needed for the clinical trials for the combined therapies.

The Pfizer Agreement will terminate upon completion of all activities outlined in the study plan and the relevant protocols. Either party may terminate the Pfizer Agreement for the uncured material breach or insolvency of the other party, if it reasonably deems it necessary in order to protect the safety, health or welfare of subjects enrolled in the clinical trials for the combined therapies due to the existence of a material safety issue, or in certain circumstances for an unresolved clinical hold with respect to either the IBRANCE® (palbociclib) or OP-1250. In addition, either party may terminate the Pfizer Agreement if certain disputes between the parties are not resolved after following the applicable dispute resolution procedures or if either party determines to discontinue clinical development for medical, scientific, legal or other reasons.

The Pfizer Agreement does not grant any right of first negotiation to participate in future clinical trials, and each of the parties retains all rights and ability to evaluate their respective compounds. Costs incurred in connection to the Pfizer Agreement are included in the research and development expense in the accompanying consolidated statements of operations and comprehensive loss for the years ended December 31, 2022, and 2021.

License Agreement

In June 2022, the Company entered into an exclusive global license agreement with Aurigene Discovery Technologies Limited (“Aurigene”) to research, develop and commercialize novel small molecule inhibitors of an undisclosed oncology target (“the Aurigene Agreement”).

Under the terms of the Aurigene Agreement, Aurigene will provide to the Company an exclusive license to its portfolio of novel small molecule inhibitors of the target. Financial terms of the Aurigene Agreement include a \$8.0 million upfront payment for rights to a pre-existing Aurigene program and potential future milestone payments of up to \$60.0 million in clinical development and regulatory milestones, and up to \$370.0 million in commercial milestones. Aurigene is also eligible to receive mid-single digits to the low double digits royalties on product sales, if any. During the research term, the Company will contribute funding to Aurigene to facilitate Aurigene’s ongoing discovery efforts. The Company and Aurigene will jointly direct further preclinical work and, if successful, the Company will lead clinical development as well as regulatory and commercial activities. The Company and Aurigene jointly own collaboration compounds and rights to any inventions made during the research term.

The term of the Aurigene Agreement will continue until the expiration of the last-to-expire of all payment obligations with respect to all licensed products thereunder, unless terminated earlier in accordance with the terms of the Aurigene Agreement. The Aurigene Agreement may be terminated (a) by the Company for

convenience, in its sole discretion, upon prior written notice to Aurigene, (b) by either the Company or Aurigene in connection with the other party's uncured material breach or (c) by either the Company or Aurigene in connection with the insolvency of the other party.

The \$8.0 million upfront payment was incurred in June 2022 and recorded as research and development expense in the accompanying consolidated statements of operations and comprehensive loss. Costs incurred and milestones payments due to Aurigene prior to regulatory approval are recognized as research and development expenses in the period incurred. Payments due to Aurigene upon or subsequent to regulatory approval will be accrued as a provision to cost of sales in the period when achievement of respective milestone target is probable. As of December 31, 2022, it was determined that it is not probable to achieve any of the milestone target, and therefore, the Company recorded zero expense related to the milestone for the year ended December 31, 2022.

Management Services Agreements

The Company conducts research and development programs internally and through third parties that include, among others, arrangements with vendors, consultants, CMOs, and CROs. The Company has contractual arrangements in the normal course of business with these parties, however, the contracts with these parties are cancelable generally on reasonable notice within one year and the Company's obligations under these contracts are primarily based on services performed through termination dates plus certain cancellation charges, if any, as defined in each of the respective agreements. In addition, these agreements may, from time to time, be subjected to amendments as a result of any change orders executed by the parties. As of December 31, 2022, the Company did not have material contractual commitments with respect to these arrangements.

Contingencies

From time to time, the Company may have certain contingent liabilities that arise in the ordinary course of business. The Company accrues a liability for such matters when it is probable that future expenditures will be made, and such expenditures can be reasonably estimated. For all periods presented, the Company was not a party to any pending material litigation or other material legal proceedings.

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its Board of Directors and executive officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. As of December 31, 2022 and 2021, respectively, the Company had not incurred any material costs as a result of such indemnifications.

13. Subsequent Event

On March 9, 2023, the Company announced a corporate restructuring and portfolio prioritization to focus its resources on the late-stage clinical development of OP-1250 for the treatment of ER+ / HER2- metastatic breast cancer. As part of this restructuring, the Company's workforce will be reduced by approximately 25%, affecting employees across research, early development, and general and administrative functions in the Company.

This workforce reduction is expected to be completed by the end of the first quarter of 2023. Affected employees will be eligible to receive severance and other benefits, contingent upon such employee's execution and the

effectiveness of a separation agreement, which includes a general release of claims against the Company. The Company estimates that these severance and other costs will result in a one-time accounting charge of approximately \$2.8 million in the first quarter of 2023, \$2.7 million of which is attributable to cash expenditures expected to be paid in the same quarter. The charges that the Company expects to incur in connection with the restructuring are subject to a number of assumptions, and actual results may differ materially. The Company may also incur additional costs not currently contemplated due to events that may occur as a result of, or that are associated with, the restructuring.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

As of December 31, 2022, management, with the participation of our Chief Executive Officer and Chief Financial Officer, performed an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. Our disclosure controls and procedures are designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including the Chief Executive Officer and Chief Financial Officer, to allow timely decisions regarding required disclosures.

Any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objective and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that, as of December 31, 2022, the design and operation of our disclosure controls and procedures were effective at a reasonable assurance level.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting for our company. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with GAAP and includes those policies and procedures that: (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of our company's assets that could have a material effect on the financial statements.

Internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements prepared for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management, with the participation of our Chief Executive Officer (principal executive officer) and Chief Operating and Financial Officer (principal financial officer), assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, our management used the criteria set forth in the Internal Control—Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on its assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2022 based on those criteria.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rules 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the fourth quarter ended December 31, 2022 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. We are continually monitoring and assessing the COVID-19 situation to minimize the impact to the design and operating effectiveness of our internal controls.

Item 9B. Other Information.

Costs Associated with Exit or Disposal Activities

On March 9, 2023, we announced a corporate restructuring and portfolio prioritization to focus our resources on the late-stage clinical development of OP-1250 for the treatment of ER+/-HER2- metastatic breast cancer. As part of this restructuring, our workforce will be reduced by approximately 25%, affecting employees across research, early development, and general and administrative functions.

This workforce reduction is expected to be completed by the end of the first quarter of 2023. Affected employees will be eligible to receive severance and other benefits, contingent upon such employee's execution and the effectiveness of a separation agreement, which includes a general release of claims against us. We estimate that these severance and other costs will result in a one-time accounting charge of approximately \$2.8 million in the first quarter of 2023, \$2.7 million of which is attributable to cash expenditures expected to be paid in the same quarter, and expect that payment of these costs will also be made in the first quarter of 2023. The charges that we expect to incur in connection with the restructuring are subject to a number of assumptions, and actual results may differ materially. We may also incur additional costs not currently contemplated due to events that may occur as a result of, or that are associated with, the restructuring.

Departure of Directors or Certain Officers; Compensatory Arrangements of Certain Officers

As part of the restructuring, each of Kinney Horn, our Chief Business Officer, and Cyrus Harmon, Ph.D., our Chief Research Officer, will cease their employment with us, effective March 24, 2023, or the Separation Date, and has entered into a separation agreement with us. Pursuant to the separation agreement entered into with Mr. Horn, subject to the effectiveness of a general release of claims, Mr. Horn will (i) receive 12 months of his base salary and medical insurance coverage premiums, plus a pro-rated portion of his target bonus for 2023, for a total of approximately \$0.5 million, less required deductions and withholdings, (ii) provide ongoing consulting and advisory services to us until such services are terminated by us or Mr. Horn pursuant to the terms of a consulting agreement, and (iii) upon the Separation Date and pursuant to the terms of his existing employment agreement with us, be entitled to accelerated vesting of options to purchase 39,384 shares of our common stock held as of the Separation Date. Pursuant to the separation agreement entered into with Dr. Harmon, subject to the effectiveness of a general release of claims, Dr. Harmon will be entitled to receive 12 months of his base salary and medical insurance coverage premiums, plus a pro-rated portion of his target bonus for 2023, for a total of approximately \$0.6 million, less required deductions and withholdings. We expect that Dr. Harmon will continue in his role as a member of our Board of Directors.

"At the Market" Equity Offering Program

On March 9, 2023, we entered into a Sales Agreement, or the ATM Agreement, with Oppenheimer & Co., Inc., or the Agent, pursuant to which we may offer and sell, from time to time through the Agent, at our option, shares of our common stock for aggregate sales proceeds of up to \$100 million, or the Shares. The issuance and sale, if any, of Shares under the ATM Agreement will be pursuant to our effective registration statement on Form S-3 (File No. 333-263117), and the related prospectus supplement dated March 9, 2023, in each case filed with the SEC.

Pursuant to the ATM Agreement, the Agent may sell the Shares in sales deemed to be “at-the-market” equity offerings as defined in Rule 415 promulgated under the Securities Act, including sales made directly on or through the Nasdaq Global Select Market. We may sell Shares in amounts and at times to be determined by us from time to time through the Agent and subject to the terms and conditions of the ATM Agreement, but we have no obligation to sell any of the Shares under the ATM Agreement. The offer and sale of the Shares pursuant to the ATM Agreement will terminate upon the earlier of (a) the issuance and sale of all of the Shares subject to the ATM Agreement or (b) the termination of the ATM Agreement.

We have agreed to pay the Agent a commission of up to 3.0% of the aggregate gross proceeds from any Shares sold by the Agent and to provide the Agent with customary indemnification and contribution rights, including for liabilities under the Securities Act. We also will reimburse the Agent for certain specified expenses in connection with entering into the ATM Agreement. The ATM Agreement contains customary representations and warranties and conditions to the placements of the Shares pursuant thereto.

The foregoing summary of the ATM Agreement does not purport to be complete and is qualified in its entirety by reference to the full text of the ATM Agreement, which is attached as Exhibit 1.1 to this Annual Report on Form 10-K. Cooley LLP, counsel to Olema, has issued a legal opinion relating to due authorization and valid issuance of the Shares, a copy of which, including the consent included therein, is attached as Exhibit 5.1 to this Annual Report on Form 10-K.

This Annual Report on Form 10-K shall not constitute an offer to sell or the solicitation of an offer to buy the Shares, nor shall there be any offer, solicitation, or sale of the Shares in any state in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not Applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Information required by this item regarding directors and director nominees, executive officers, the board of directors and its committees, and certain corporate governance matters is incorporated by reference to the information set forth under the captions “Proposal No. 1—Election of Directors,” “Corporate Governance and Board of Directors Matters” and “Executive Officers” in our Proxy Statement for our 2023 Annual Meeting of Stockholders. Information required by this item regarding compliance with Section 16(a) of the Exchange Act, if applicable, is incorporated by reference to the information set forth under the caption “Delinquent Section 16(a) Reports” in our Proxy Statement.

Our written code of business conduct and ethics (the “Code of Conduct”) applies to all of our employees, officers and directors, including our principal executive officer, principal financial officer and principal accounting officer or controller. The Code of Conduct is available on our corporate website at <https://www.olema.com/> in the Investors & Media section under “Corporate Governance.” If we make any substantive amendments to our Code of Conduct or grant any of our directors or executive officers any waiver, including any implicit waiver, from a provision of our Code of Conduct, we will disclose the nature of the amendment or waiver on our website or in a Current Report on Form 8-K. Information contained in, or that can be accessed through, our website is not incorporated by reference herein, and you should not consider information on our website to be part of this Annual Report.

Item 11. Executive Compensation.

Information required by this item regarding executive compensation is incorporated by reference to the information set forth under the captions “Executive Compensation” and “Director Compensation” in our Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

Information required by this item regarding security ownership of certain beneficial owners and management is incorporated by reference to the information set forth under the caption “Security Ownership of Certain Beneficial Owners and Management” and “Equity Compensation Plan Information” in our Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

Information required by this item regarding certain relationships, related transactions and director independence is incorporated by reference to the information set forth under the caption “Transactions with Related Persons and Indemnification” and “Corporate Governance and Board Matters” in our Proxy Statement.

Item 14. Principal Accountant Fees and Services.

Information required by this item regarding principal accounting fees and services is incorporated by reference to the information set forth under the caption “Proposal No. 4—Ratification of Selection of Independent Registered Public Accounting Firm” in our Proxy Statement.

PART IV

Item 15. Exhibit and Financial Statement Schedules.

(a) The following documents are filed as part of this Annual Report:

1. *Consolidated Financial Statements*. See Index to Consolidated Financial Statements in Part II Item 8 of this Annual Report.
2. *Consolidated Financial Statement Schedules*. None. All financial statement schedules are omitted because they are not applicable, not required under the instructions, or the requested information is included in the financial statements or notes thereto.
3. *Exhibits*. The following is a list of exhibits filed with this Annual Report or incorporated herein by reference:

Exhibit Number	Exhibit Description	Incorporation by Reference				
		Form	File No.	Exhibit	Filing Date	Filed Herewith
1.1	Sales Agreement by and between Registrant and Oppenheimer & Co. Inc., dated March 9, 2023.					X
3.1	Amended and Restated Certificate of Incorporation.	8-K	001-39712	3.1	11/23/2020	
3.2	Amended and Restated Certificate of Bylaws.	8-K	001-39712	3.1	12/16/2022	
4.1	Form of Common Stock Certificate.	S-1	333-249748	4.1	10/30/2020	
4.2	Amended and Restated Investors' Rights Agreement, by and among the Registrant and certain of its stockholders, dated September 30, 2020.	S-1	333-249748	4.2	10/30/2020	
4.3	Description of Capital Stock.	10-K	001-39712	4.3	3/17/2021	
5.1	Opinion of Cooley LLP.					X
10.1#	Olema Pharmaceuticals, Inc. 2014 Stock Plan, as amended.	S-1	333-249748	10.1	10/30/2020	
10.2#	Forms of Stock Option Grant Notice, Stock Option Agreement, Early Exercise Stock Purchase Agreement and Notice of Exercise and Restricted Stock Award Grant Notice and Restricted Stock Award Agreement under the Olema Pharmaceuticals, Inc. 2014 Stock Plan.	S-1	333-249748	10.2	10/30/2020	
10.3#	Olema Pharmaceuticals, Inc. 2020 Equity Incentive Plan.	S-1/A	333-249748	10.3	11/16/2020	

Exhibit Number	Exhibit Description	Incorporation by Reference				
		Form	File No.	Exhibit	Filing Date	Filed Herewith
10.4#	Forms of Stock Option Grant Notice and Stock Option Agreement under the Olema Pharmaceuticals, Inc. 2020 Equity Incentive Plan.	S-1	333-249748	10.4	10/30/2020	
10.5#	Forms of Restricted Stock Unit Grant Notice and Restricted Stock Unit Award Agreement under the Olema Pharmaceuticals, Inc. 2020 Equity Incentive Plan.	S-1	333-249748	10.5	10/30/2020	
10.6#	Olema Pharmaceuticals, Inc. 2020 Employee Stock Purchase Plan.	S-1/A	333-249748	10.6	11/16/2020	
10.7#	Olema Pharmaceuticals, Inc. 2020 Non-Employee Director Compensation Policy.	S-1/A	333-249748	10.7	11/16/2020	
10.8#	Form of Indemnification Agreement by and between the Registrant and its directors and executive officers.	S-1	333-249748	10.8	10/30/2020	
10.9#	Amended and Restated Offer Letter by and between the Registrant and Sean Bohlen, dated November 13, 2020.	S-1/A	333-249748	10.9	11/16/2020	
10.10#	Amended and Restated Offer Letter by and between the Registrant and Cyrus L. Harmon, dated November 13, 2020.	S-1/A	333-249748	10.10	11/16/2020	
10.11#	Amended and Restated Offer Letter by and between the Registrant and Kinney Horn, dated November 13, 2020.	S-1/A	333-249748	10.11	11/16/2020	
10.12#	Amended and Restated Offer Letter by and between the Registrant and Shane Kovacs, dated November 13, 2020.	S-1/A	333-249748	10.12	11/16/2020	
10.13#	Amended and Restated Offer Letter by and between the Registrant and Peter Kushner, dated November 13, 2020.	S-1/A	333-249748	10.13	11/16/2020	
10.14#	Amended and Restated Offer Letter by and between the Registrant and David Myles, dated November 13, 2020.	S-1/A	333-249748	10.14	11/16/2020	

Exhibit Number	Exhibit Description	Incorporation by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.15#	Amended and Restated Offer Letter by and between the Registrant and John B. Moriarty, Jr., dated November 13, 2020.	S-1/A	333-249748	10.15	11/16/2020	
10.16	Clinical Collaboration and Supply Agreement by and between the Registrant and Novartis Institutes for BioMedical Research, Inc., dated July 22, 2020.	S-1	333-249748	10.16	10/30/2020	
10.17#	Olema Pharmaceuticals, Inc. 2022 Inducement Plan	10-K	001-39712	10.17	2/28/2022	
10.18#	Form of Stock Option Agreement and Option Grant Notice under the Inducement Plan.	10-K	001-39712	10.18	2/28/2022	
10.19#	Offer Letter by and between the Registrant and Naseem Zojwalla, dated December 15, 2021.	10-K	001-39712	10.19	2/28/2022	
10.20¥	Drug Discovery Collaboration and License Agreement by and between the Registrant and Aurigene Discovery Technologies Limited, dated June 7, 2022.	10-Q	001-39712	10.1	8/9/2022	
21.1	Subsidiaries of the Registrant as of December 31, 2022.					X
23.1	Consent of Independent Registered Public Accounting Firm.					X
23.2	Consent of Cooley LLP (included in Exhibit 5.1).					X
24.1	Power of Attorney (included on the Signatures page of this Annual Report on Form 10-K).					X
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					X

Exhibit Number	Exhibit Description	Incorporation by Reference			Filed Herewith
		Form	File No.	Exhibit	
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				X
32.1†	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X
32.2†	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X
101.INS	XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL Document				X
101.SCH	XBRL Taxonomy Extension Schema Document				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document				X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document				X
104	Cover Page Interactive Data File – The cover page interactive data file does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document				X

Indicates management contract or compensatory plan or arrangement.

† The certifications attached as Exhibit 32.1 and Exhibit 32.2 that accompany this Annual Report on Form 10-K are not deemed filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of the Registrant under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Annual Report on Form 10-K, irrespective of any general incorporation language contained in such filing.

¥ Pursuant to Item 601(b)(10) of Regulation S-K, portions of this exhibit have been omitted as the Registrant has determined that the omitted information is the type that the Registrant customarily and actually treats as private or confidential and is not material.

Item 16. Form 10-K Summary.

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Olema Pharmaceuticals, Inc.

Date: March 9, 2023

By: /s/ Sean Bohan, M.D., Ph.D.

Sean Bohan, M.D., Ph.D.

Chief Executive Officer

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Olema Pharmaceuticals, Inc.

Date: March 9, 2023

By: /s/ Shane Kovacs

Shane Kovacs

Chief Operating and Financial Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Sean Bohan, M.D., Ph.D. and Shane Kovacs, and each of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution for him or her, and in his or her name in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith, with the U.S. Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, and either of them, his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Name	Title	Date
<u>/s/ Sean Bohan, M.D., Ph.D.</u> Sean Bohan, M.D., Ph.D.	President, Chief Executive Officer and Director <i>(Principal Executive Officer)</i>	March 9, 2023
<u>/s/ Shane Kovacs</u> Shane Kovacs	Chief Operating and Financial Officer <i>(Principal Financial and Accounting Officer)</i>	March 9, 2023
<u>/s/ Ian Clark</u> Ian Clark	Director	March 9, 2023
<u>/s/ Cynthia Butitta</u> Cynthia Butitta	Director	March 9, 2023
<u>/s/ Cyrus L. Harmon</u> Cyrus L. Harmon	Director	March 9, 2023
<u>/s/ Sandra J. Horning, M.D.</u> Sandra J. Horning, M.D.	Director	March 9, 2023
<u>/s/ Gorjan Hrustanovic, Ph.D.</u> Gorjan Hrustanovic, Ph.D.	Director	March 9, 2023
<u>/s/ Yi Larson</u> Yi Larson	Director	March 9, 2023
<u>/s/ Andrew Rappaport</u> Andrew Rappaport	Director	March 9, 2023
<u>/s/ Graham Walmsley, M.D., Ph.D.</u> Graham Walmsley, M.D., Ph.D.	Director	March 9, 2023

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-250209, 333-254403, and 333-263114) pertaining to the 2020 Equity Incentive Plan, 2020 Employee Stock Purchase Plan, and 2022 Inducement Plan of Olema Pharmaceuticals, Inc. of our report dated March 9, 2023, with respect to the consolidated financial statements of Olema Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) of Olema Pharmaceuticals, Inc. for the year ended December 31, 2022.

/s/ Ernst & Young LLP

Iselin, New Jersey
March 9, 2023

**CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Sean Bohan, M.D., Ph.D., certify that:

1. I have reviewed this Annual Report on Form 10-K of Olema Pharmaceuticals, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 9, 2023

By: /s/ Sean Bohan, M.D., Ph.D.

Sean Bohan, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

**CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Shane Kovacs, certify that:

1. I have reviewed this Annual Report on Form 10-K of Olema Pharmaceuticals, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
 - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 9, 2023

By: /s/ Shane Kovacs

Shane Kovacs
Chief Operating and Financial Officer
(Principal Financial and Accounting Officer)

**CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report of Olema Pharmaceuticals, Inc. (the “Company”) on Form 10-K for the period ended December 31, 2022 as filed with the Securities and Exchange Commission on the date hereof (the “Report”), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 9, 2023

By: /s/ Sean Bohan, M.D., Ph.D.

Sean Bohan, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

**CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report of Olema Pharmaceuticals, Inc. (the "Company") on Form 10-K for the period ended December 31, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

- (1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 9, 2023

By: /s/ Shane Kovacs

Shane Kovacs
Chief Operating and Financial Officer
(Principal Financial and Accounting Officer)

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