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

FORM 10-K

(Mark One)

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

For the fiscal year ended: December 31, 2024

☐ **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: 001-36167

KARYOPHARM THERAPEUTICS INC.

(Exact name of registrant as specified in its charter)

Delaware	**26-3931704**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

85 Wells Avenue, 2nd Floor, Newton, Massachusetts 02459
(Address of principal executive offices) (zip code)

Registrant's telephone number, including area code: (617) 658-0600

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

Title of each class	Trading Symbol(s)	Name of each exchange on which listed
Common Stock, $0.0001 par value	**KPTI**	**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 ☐	Accelerated filer ☒
Non-accelerated filer ☐	Smaller reporting company ☒
	Emerging growth company ☐

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-2of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the common stock was last sold on June 30, 2024 was approximately $107.6 million. Shares of common stock held by each executive officer and director and by each holder of 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

Number of shares outstanding of the registrant's Common Stock as of February 14, 2025: 126,240,054.

Documents incorporated by reference:

Portions of the registrant's Proxy Statement for its 2025 Annual Meeting of Stockholders, which the registrant intends to file with the Securities and Exchange Commission no later than 120 days after the registrant's fiscal year end of December 31, 2024, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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Forward-Looking Information

This Annual Report on Form 10-K contains forward-looking statements regarding the expectations of Karyopharm Therapeutics Inc., herein referred to as "Karyopharm," the "Company," "we," or "our," with respect to the possible achievement of discovery and development milestones, our future discovery and development efforts, including regulatory submissions and approvals, our commercialization efforts, our partnerships and collaborations with third parties, our future operating results and financial position, our ability to continue as a going concern, our business strategy, and other objectives for future operations. We often use words such as "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify these forward-looking statements by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause actual results or events to differ materially from those indicated by forward-looking statements. These risks and uncertainties include, but are not limited to, those described in "Part I—Item 1A. Risk Factors" of this Annual Report on Form 10-K and under the heading "Summary of Risk Factors" below. As a result of these and other factors, we may not actually achieve the plans, intentions, expectations or results disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

References to XPOVIO® (selinexor) also refer to NEXPOVIO® (selinexor) when discussing its approval and commercialization in certain countries or territories outside of the U.S.

Summary of Risk Factors

Below is a summary of the principal factors that make an investment in our common stock speculative or risky. This summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found below under the heading "Risk Factors" and should be carefully considered, together with other information in this Annual Report on Form 10-K and our other filings with the SEC, before making an investment decision regarding our common stock.

- If we or our collaborators are unable to successfully commercialize current and future indications of XPOVIO or other products or product candidates, our business, financial condition and future profitability will be materially harmed.
- XPOVIO faces substantial competition.
- If our clinical trials fail to demonstrate safety and effectiveness to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs, experience delays or be unable to complete the development of such product candidates.
- We may be unable to successfully enroll patients in our ongoing and planned clinical trials in a reasonable timeframe, or at all.
- Serious adverse or unacceptable side effects related to XPOVIO, our product candidates or future products may delay or prevent their regulatory approval, cause us to suspend or discontinue clinical trials, or limit the commercial value of our approved indications.
- The results of previous clinical trials may not be predictive of future trial results and interim or top-line data may be subject to change or qualification.
- We may not be successful in our efforts to identify or discover additional potential product candidates, or our decisions to prioritize the development of certain product candidates over others may later prove wrong.
- We may not be able to maintain or expand our sales, marketing and distribution capabilities in order to successfully commercialize XPOVIO or any of our products or product candidates, if approved.
- Any business that we or our collaborators conduct outside of the U.S. may be adversely affected by international risks and uncertainties.
- We or our collaborators may not receive regulatory approvals for the commercialization of some or all of our or their product candidates, including necessary companion diagnostic devices, in a timely manner, or at all.
- We or our collaborators may not be able to utilize accelerated development pathways to obtain regulatory approval, orphan drug exclusivity or certain other designations for our or their product candidates, which may result in delays receiving necessary marketing approvals.
- Our or our collaborators' ability to commercialize our or their products may be limited by the terms of their respective regulatory approvals and ongoing regulation of our products.
- Our failure to comply with post-approval development and regulatory requirements, pricing regulations, reporting and payment obligations under governmental drug pricing programs, applicable healthcare, privacy and data security laws and environmental, health and safety laws and regulations may have a material adverse effect on our business, financial condition or results of operations.
- Changes in U.S. and international trade policies, particularly with respect to China, may adversely impact our business.
- We may not be able to continue as a going concern.
- We may never achieve or maintain profitability and will need additional funding to achieve our business objectives.
- We may not be able to satisfy our indebtedness, on a timely basis or at all.
- Our business, financial condition and stock price may be impacted by unstable market and economic conditions.
- Our dependence on third parties for certain aspects of our business, such as clinical development, manufacturing, marketing, distribution and/or commercialization of XPOVIO and/or our product candidates, could negatively impact our development and commercialization plans.
- If we are unable to obtain and maintain patent protection for our products and product candidates and other discoveries, or the scope of the patent protection obtained is not sufficiently broad, our ability to successfully commercialize our products or product candidates may be adversely affected.

- We may become involved in lawsuits to protect or enforce our intellectual property rights, or third parties may initiate legal proceedings against us alleging our infringement of their intellectual property rights.
- If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.
- Information technology system failures or security breaches may materially adversely affect our business and operations.
- The price of our common stock has been and may continue to be volatile and if we fail to maintain compliance with Nasdaq our common stock could be delisted.
- Securities or other litigation could result in substantial costs and may divert management's time and attention from our business.

PART I

Item 1. Business

Overview

We are a commercial-stage pharmaceutical company pioneering novel cancer therapies and dedicated to the discovery, development and commercialization of first-in-class drugs directed against nuclear export for the treatment of cancer. Our scientific expertise is based upon an understanding of the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing and commercializing novel, small molecule Selective Inhibitor of Nuclear Export ("SINE") compounds that inhibit the nuclear export protein exportin 1 ("XPO1"). These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases with high unmet medical need. Our lead asset, XPOVIO® (selinexor), was the first oral XPO1 inhibitor to receive marketing approval, receiving its initial U.S. approval from the U.S. Food and Drug Administration ("FDA") in July 2019, and is currently approved and marketed in the U.S. for the following indications:

- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Approval in this indication was based on the results from the BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) trial (the "BOSTON Trial");
- In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors ("PIs"), at least two immunomodulatory agents ("IMiDs"), and an anti-CD38 monoclonal antibody ("mAb"). We refer to myeloma that is refractory to these five agents as penta-refractory. Approval in this indication was based on the results from the STORM (**S**elinexor **T**reatment of **R**efractory **My**eloma) trial (the "STORM Trial"); and
- For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma ("DLBCL"), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. This indication was approved under accelerated approval based on response rate and was based on the results from the SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) trial (the "SADAL Trial"). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The commercialization of XPOVIO in the U.S. is currently supported by sales representatives, nurse liaisons, and a market access team, as well as KaryForward®, an extensive patient and healthcare provider support program. Our commercial efforts are also supplemented by patient support initiatives coordinated by our dedicated network of participating specialty pharmacy providers. We plan to continue to educate physicians, other healthcare providers and patients about XPOVIO's clinical profile and unique mechanism of action as we continue to expand XPOVIO use.

The commercialization of XPOVIO and NEXPOVIO® (selinexor) (the brand name for selinexor in Europe and the United Kingdom ("UK")) outside of the U.S. is managed by our partners in their respective territories, as described under "*Collaborations*" below. XPOVIO/NEXPOVIO has received regulatory approval in various indications in over 45 countries outside the U.S. and is commercially available in a growing number of countries as our partners continue to secure reimbursement approvals.

Our primary focus is on marketing XPOVIO in its currently approved indications as well as developing and seeking the regulatory approval of selinexor as an oral agent targeting multiple high unmet need cancer indications, including our lead clinical programs in myelofibrosis and our other late-stage clinical programs in endometrial cancer and multiple myeloma. We plan to continue to conduct clinical trials and to seek additional approvals for the use of selinexor as a single agent or in combination with other oncology therapies to expand the patient populations that are eligible for treatment with selinexor. As announced in January 2024, further clinical development of our eltanexor program continues to remain on hold in an effort to focus our resources on our prioritized late-stage programs.

In May 2024, we entered into a series of transactions (the "Refinancing Transactions") to limit our aggregate indebtedness, extend the maturity of certain of our indebtedness and provide us with additional working capital. Pursuant to these transactions, we borrowed $100.0 million from existing lenders and certain entities managed by HealthCare Royalty Management, LLC ("HCRx") under a new, senior secured term loan facility and used a portion of the proceeds of that loan to repay obligations under our existing financing arrangement with HCRx pursuant to an amendment that made other changes to our existing financing arrangement with HCRx. We also exchanged, pursuant to privately negotiated agreements, an aggregate principal amount of $148.0 million of our existing 3.00% unsecured convertible senior notes for (i) $111.0 million aggregate principal amount of new 6.00% secured convertible senior notes and (ii) warrants to purchase up to 45.8 million shares of our common stock. In addition, HCRx purchased $5.0 million aggregate principal amount of new 6.00% secured convertible senior notes through satisfaction of $5.0 million of our existing

obligations to HCRx. Please refer to Note 10, "*Long-Term Obligations*", to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K for additional details of the Refinancing Transactions.

As of December 31, 2024, we had an accumulated deficit of $1.6 billion. We had net losses of $76.4 million and $143.1 million for the years ended December 31, 2024 and 2023, respectively. We recognized total revenue of $145.2 million in 2024, including $112.8 million of XPOVIO net product revenue and $32.4 million of license revenue. As of December 31, 2024, we had $108.7 million in cash, cash equivalents and investments. Based on our current business plan and current capital resources, combined with the uncertainty regarding the availability of additional funding and considering our debt obligations, including a requirement to maintain cash, cash equivalents and investments of at least $25.0 million at all times, we have concluded that there is substantial doubt regarding our ability to continue as a going concern within one year after the date the accompanying consolidated financial statements are issued. See "*Liquidity, Capital Resources, and Going Concern*" in Part II, "*Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations*", below for a further discussion of our liquidity and the conditions that raise substantial doubt regarding our ability to continue as a going concern.

Our Strategy

At Karyopharm we are passionate about our mission to positively impact patient lives and defeat cancer. With our first-in-class SINE technology, our foundation is in our science. Our vision is to be a leading innovator that develops and commercializes transformative medicines for patients and society. There are four key pillars that we believe will drive our underlying value and provide significant market opportunities for us.

- ***Maximize the Commercial Value of XPOVIO in Multiple Myeloma.*** We are building upon our existing U.S. multiple myeloma foundation as we continue to expand the breadth and depth of XPOVIO's use across lines of therapy in the relapsed/refractory setting, focusing on growing sales in our approved U.S. indications by establishing XPOVIO as a novel effective modality. With our partners, we plan to maximize the global opportunity to bring XPOVIO to patients worldwide.
- ***Focus on our Prioritized Clinical Pipeline.*** Our science enables us to potentially make a big difference in the lives of patients. We are focused on advancing our lead clinical programs in myelofibrosis and our other late-stage clinical programs in endometrial cancer and multiple myeloma. Our clinical pipeline has been consciously and strategically focused to target cancers with high unmet need based on the potential to provide meaningful clinical benefit to patients and compelling supportive data. We will also continue to expand our understanding of the role nuclear transport plays in the underlying biology of cancer through focused signal seeking activities, which primarily include preclinical activities, to identify future opportunities in other oncology indications for our SINE technology that may provide support for future clinical investigation.
- ***Provide Strong Leadership.*** We believe we have the right people in place and a strong leadership team with the ability to help position us to achieve scientific, clinical and commercial goals and to execute on our key corporate objectives. We strive to be a top-talent destination for those who desire to make a difference in patients' lives.
- ***Maintain a Well-capitalized Business to Execute our Core Objectives.*** We are focused on maintaining a well-capitalized business that will enable the advancement of our clinical development opportunities.

Our Programs to Treat Cancer

Overview

Cancer cells develop when there is dysregulation of genes and proteins that regulate critical cellular behaviors, such as cell growth and survival. This dysregulation of cellular function is most often due to damage to DNA. Proteins called tumor suppressor proteins can monitor genes encoded in DNA/gene mutations for damage, and if damage is detected, the tumor suppressor proteins will direct the cell to attempt to repair it, or if the DNA damage is too severe, the tumor suppressor proteins will direct the cell to die in a process called apoptosis. In this way tumor suppressor proteins can prevent healthy cells that acquire DNA damage from turning into cancer cells, and thus cancer cells need to functionally inactivate tumor suppressor proteins in order to survive.

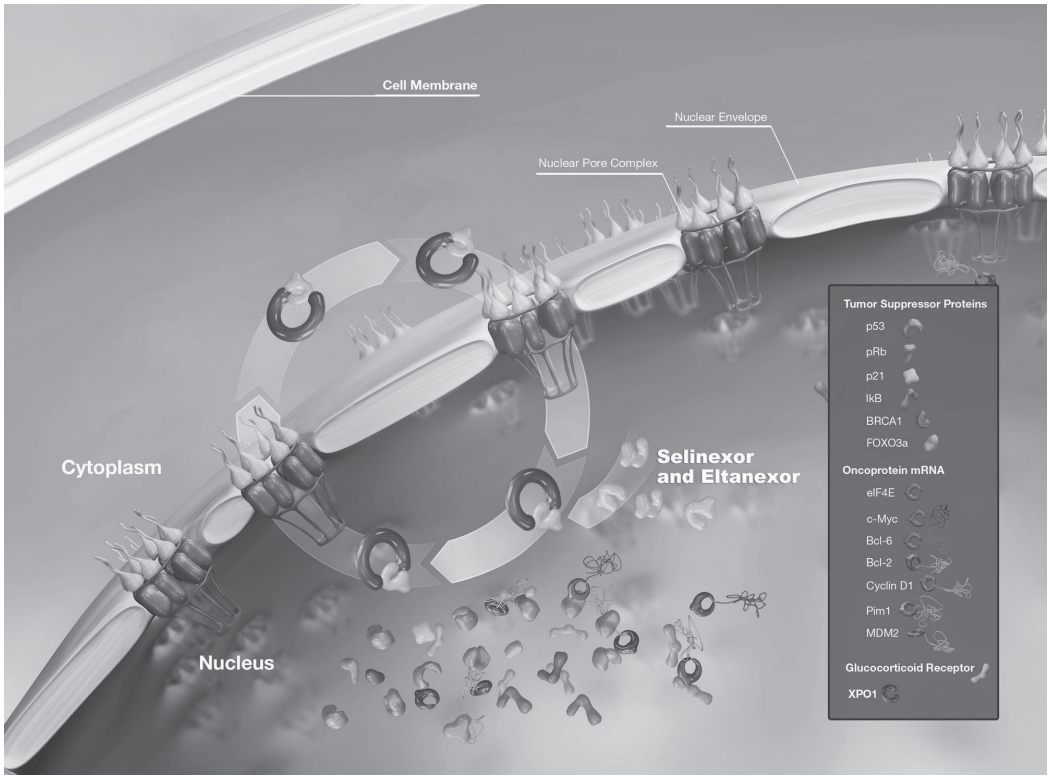
Cells contain different compartments that organize their components. The nucleus contains DNA, and is separated from the area outside of the nucleus, called the cytoplasm, by the nuclear membrane. Since many tumor suppressor proteins physically need to interact with DNA, they can only function properly when they are located inside of a cell's nucleus. Proteins, however, are not made inside the nucleus but rather in the cytoplasm. Larger nuclear proteins, including many tumor suppressor proteins, must be transported from the cytoplasm into the nucleus to perform their functions in keeping a cell healthy. Similarly, these proteins can also be exported back into the cytoplasm. Proteins move from the nucleus to the cytoplasm through a protein complex embedded in the nuclear membrane called the nuclear pore. The nuclear pore works like a gate through which large molecules (also called "macromolecules"),

including many proteins and ribonucleic acids, enter and exit the nucleus. When molecules enter the nucleus from the cytoplasm, the process is called import, and when molecules exit from the nucleus to the cytoplasm, the process is called export. The import and export of most proteins and other large molecules between the nucleus and cytoplasm require specific carrier proteins to chaperone their cargo molecules through the nuclear pore complex. Carrier proteins, which mediate the import of macromolecules into the nucleus, are called importins, and those which mediate the export of macromolecules out of the nucleus are called exportins. Therefore, the processes of import and export are carried out separately and are typically regulated independently.

One way that cancers functionally inactivate tumor suppressor proteins is via overproduction of a specific transport protein called XPO1. XPO1 is one of eight exportins that have been identified in human cells, and it exports hundreds of proteins referred to as its "cargo proteins." In particular, XPO1 appears to be the sole exporter for many critical tumor suppressor proteins that function in the cell nucleus, including p53, p73, p21, p27, APC, FOXO, pRB and survivin. In addition to exporting tumor suppressor proteins out of the nucleus, XPO1 mediates the nuclear export of a protein called eukaryotic initiation factor 4E, which itself binds to the messenger ribonucleic acids ("mRNAs") that encode many growth-regulating proteins (also called "oncoproteins"), including c-myc, bcl-2, bcl-6 and cyclin D. XPO1 carries these oncoprotein encoding mRNAs from the nucleus into the cytoplasm where they are translated into proteins that promote cancer cell growth, invasion and survival. XPO1 also exports the anti-inflammatory (and anti-tumor) protein IκB, which inhibits a protein called NF-κB. NF-κB is found in the nucleus of most cancer cells and plays a role in cancer metastasis and chemotherapy resistance, as well as in many inflammatory and autoimmune diseases.

Mechanism of Action of Our SINE Compounds - Inhibition of XPO1

Selinexor and eltanexor are novel therapies that are oral SINE compounds specifically designed to force nuclear accumulation of multiple tumor suppressor proteins that function in the nucleus. Selinexor and eltanexor also force nuclear accumulation of growth promoting mRNAs by similarly preventing their export, which prevents the translation of these mRNAs into proteins and thereby lowers expression of the oncogenic proteins that these mRNAs encode. Additionally, blocking XPO1 leads to increased glucocorticoid receptor transcriptional activity in the nucleus, thus amplifying corticosteroid effects in sensitive tumor cells. The forced nuclear retention of these proteins can counteract a multitude of the cancer-promoting pathways that allow cancer cells with gene dysregulation to continue to grow, divide and invade tissues in an unrestrained fashion. Because normal cells have little or no DNA damage to cause gene dysregulation, accumulation of tumor suppressor proteins in their nucleus generally does not lead to apoptosis. The figure below depicts the process by which our SINE compounds inhibit the XPO1-mediated nuclear export of tumor suppressor proteins, oncoprotein mRNAs and the glucocorticoid receptor.

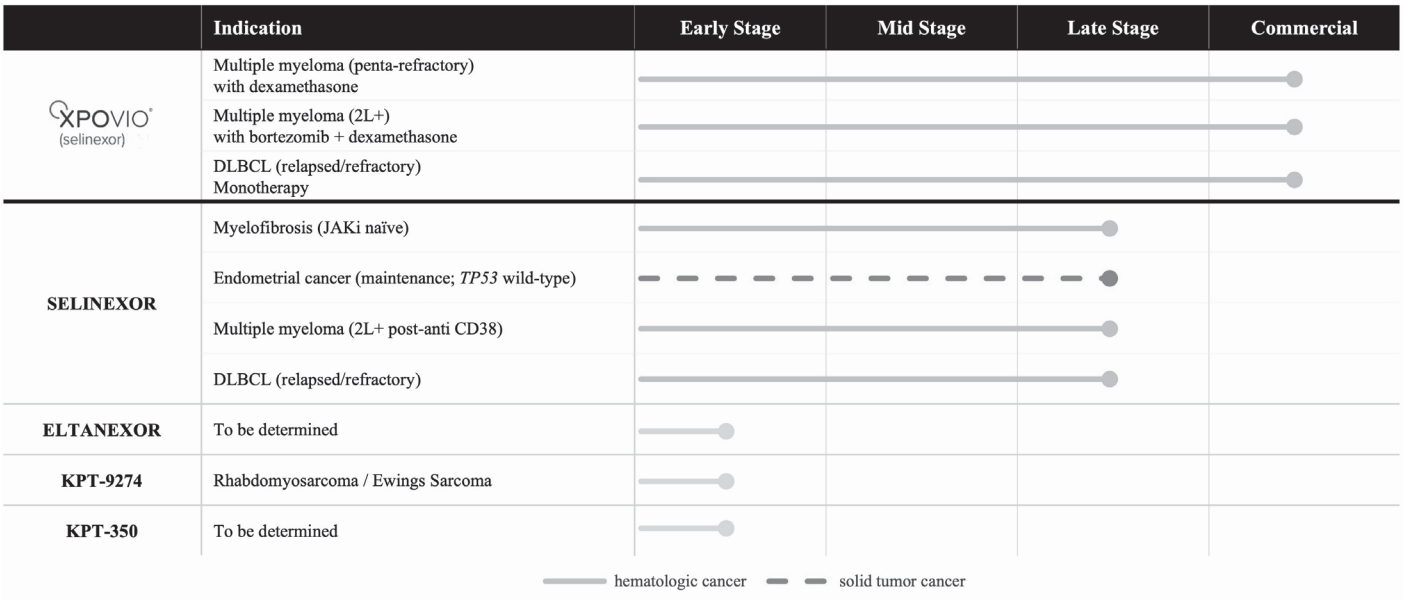


We believe that the unique mechanism of action, oral administration and low levels of major organ toxicities observed to date in patients treated with our SINE compounds, along with encouraging efficacy data, support the potential for their broad use across many cancer types, including both hematological and solid tumor malignancies. Unlike many other targeted therapeutic approaches that only work for a specific set of cancers or in a specific subgroup of patients, we believe that by restoring tumor suppressor proteins to the nucleus where they can access a cell's DNA, our SINE compounds may provide therapeutic benefits across a broad range of cancer types and can potentially benefit a wider range of patients. Additionally, and as supported by their unique mechanism of action, and preclinical, clinical and post-approval data, we believe that our SINE compounds have shown additive or synergistic benefit with approved and experimental therapies in treating cancer patients and, therefore, have the potential to serve as a backbone therapy across multiple hematological and solid tumor malignancies as part of a variety of combination therapies.

Our Pipeline and Key Clinical Trials

Oral selinexor is being evaluated in multiple clinical trials in patients with hematological and solid tumor malignancies, the majority of which are in mid to late-stage. In general, relapsed disease is cancer that returns after a period of remission and refractory disease refers to cancer that does not respond to standard treatments.

Our key selinexor clinical trials and certain early-stage pipeline programs, which are currently paused to prioritize our late-stage programs, are summarized in the chart below. In addition to these studies, there are multiple ongoing investigator-sponsored clinical trials being conducted in a variety of hematological and solid tumor malignancies as well as clinical trials pursuant to post-marketing requirements.



OUR SELINEXOR PROGRAM

We are currently evaluating selinexor in certain hematological and solid tumor malignancies, including myelofibrosis, endometrial cancer, multiple myeloma, and DLBCL.

Myelofibrosis

Overview

Myelofibrosis is a rare blood cancer which results in excessive scar tissue (fibrosis) in the bone marrow and impairs its ability to produce normal blood cells, leading to severe anemia, low platelet counts, and abnormal white blood cell production. In addition, blood cell production commonly moves to the spleen (causing spleen enlargement) or to other areas of the body. It is estimated that there are approximately 5,000 new cases of myelofibrosis each year in the U.S. and approximately 20,000 patients in the U.S. living with myelofibrosis. Although myelofibrosis can occur at any age, it is more common in older patients, with a median age at diagnosis of approximately 65 years. During the course of the disease, myelofibrosis patients can experience abdominal discomfort from increasing spleen and liver size, itching, night sweats, abnormal bleeding, fever, bone or joint pain and involuntary weight loss. The underlying causes of primary myelofibrosis are not clear; however, myelofibrosis is associated with specific well-described DNA changes (mutations) in certain genes.

There is currently no drug therapy that can cure myelofibrosis. Allogeneic hematopoietic stem cell transplantation ("HSCT") is currently the only treatment for myelofibrosis that can provide a clinical cure; patients who are not good candidates for HSCT are treated with a JAK2 inhibitor ("JAKi"), such as ruxolitinib, fedratinib, pacritinib or momelotinib to reduce spleen volume and improve symptoms. Not all patients respond adequately to a JAKi. Some patients cannot tolerate treatment or develop rapid progression on this treatment, and nearly all patients will eventually have disease progression even after a response to a JAKi. We believe there is a high unmet need for alternative treatments for myelofibrosis, such as selinexor, with a different mechanism of action, as a monotherapy and in combination with JAKi to overcome resistance to JAKi and to provide improvement in primary disease management.

In May 2022, the FDA granted selinexor Orphan Drug Designation for the treatment of myelofibrosis, and in October 2022, the European Commission granted Orphan Medicinal Product Designation for selinexor for the treatment of myelofibrosis. In addition, in July 2023, we received Fast Track Designation from the FDA for selinexor for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-essential thrombocythemia myelofibrosis, and post-polycythemia vera myelofibrosis.

The SENTRY Trial

In mid-2023, we initiated the pivotal Phase 3 part of our Phase 1/3 clinical trial to evaluate the efficacy and safety of once-weekly selinexor in combination with once or twice-daily ruxolitinib versus placebo plus ruxolitinib in JAKi-naive myelofibrosis patients (the "SENTRY Trial"; NCT04562389). The Phase 3 part of the SENTRY Trial (the "Phase 3 SENTRY Trial") is a randomized, double-blind, placebo-controlled trial, which is currently expected to enroll 350 JAKi-naive patients with intermediate or high-risk myelofibrosis. Patients are randomized 2:1 to 60 mg of selinexor plus ruxolitinib or placebo plus ruxolitinib. The ruxolitinib dose is determined by the investigators based on the patients' baseline platelet count per the drug's prescribing information. Following alignment with the FDA in late 2024, one of the co-primary endpoints in the Phase 3 SENTRY Trial was changed from total symptom score reduction of ≥50% ("TSS50") at week 24 to the absolute mean change in total symptom score ("Abs-TSS") over 24 weeks relative to baseline. The other co-primary endpoint of spleen volume response ("SVR") rate ≥ 35% ("SVR35") at week 24 was unchanged. These two co-primary endpoints will be tested sequentially beginning with SVR35 and followed by Abs-TSS. Abs-TSS measures the average improvement in patient symptom scores over 24 weeks relative to the patient's baseline symptom score and is viewed by certain key opinion leaders and patient advocacy organizations as a more accurate assessment of symptom improvement in head-to-head combination clinical trials, such as the Phase 3 SENTRY Trial, relative to TSS50. In addition, in connection with the change in co-primary endpoint, we increased the total sample size from 306 patients to 350 patients in order to analyze the new co-primary endpoint, Abs-TSS, in a sufficient number of patients. We expect to complete enrollment of the SENTRY Trial in the first half of 2025 and report top-line data in the second half of 2025.

Our evaluation of selinexor to treat patients with myelofibrosis is supported by the Phase 1 part of the SENTRY Trial, an open-label, multi-center trial of selinexor to evaluate the safety, effectiveness and recommended dose for selinexor in combination with ruxolitinib in JAKi-naïve patients with myelofibrosis (the "Phase 1 SENTRY Trial"). Enrollment in the Phase 1 SENTRY Trial was completed in August 2022. In the dose escalation portion of the Phase 1 SENTRY Trial, we evaluated selinexor at both the 40 mg and 60 mg doses in combination with ruxolitinib in JAKi-naïve patients with myelofibrosis.

Data from the Phase 1 SENTRY Trial were presented in December 2023 at the 65th American Society of Hematology 2023 Annual Meeting and Exposition. The data presented were based on results as of August 1, 2023 from 24 patients who had been assigned to either a 40 mg or 60 mg once weekly dose of selinexor, in combination with ruxolitinib 15/20 mg twice daily. At week 24, 92% of efficacy evaluable patients (11 out of 12) demonstrated SVR35 and 78% of the evaluable patients for symptom response (7 out of 9) achieved TSS50. At week 24, 79% of intent to treat ("ITT") patients (11 out of 14) achieved SVR35 and 58% of the ITT patients (7 out of 12) achieved TSS50. Patients receiving a 60 mg dose of selinexor in the Phase 1 SENTRY Trial (14 out of 24) and who achieved SVR35 and TSS50 at week 24 continued to remain in radiographic response as of the August 1, 2023 data cut-off date,

representing a median duration of 32 weeks and 51 weeks for SVR35 and TSS50 durability, respectively. The safety data as of the August 1, 2023 data-cutoff was consistent with prior data from the Phase 1 SENTRY Trial. The most common treatment-emergent adverse events ("TEAEs") for patients who received the 60 mg dose of selinexor were nausea (79%), anemia (64%), thrombocytopenia (64%) and fatigue (57%), the majority of which were grades 1-2. The most common reported grade 3-4 TEAEs for patients who received the 60 mg dose of selinexor were anemia (43%) and thrombocytopenia (29%). There were two treatment-related discontinuations, one due to thrombocytopenia and one due to peripheral neuropathy.

The SENTRY-2 Trial

In mid-2024, we initiated a Phase 2 clinical trial to evaluate the safety and efficacy of selinexor as a monotherapy in patients with JAKi-naïve myelofibrosis with moderate thrombocytopenia (the "SENTRY-2 Trial"; NCT05980806). The SENTRY-2 Trial is currently enrolling approximately 29 patients who will receive 60 mg of selinexor as a monotherapy (the "60 mg cohort") and will be followed by an additional 29 patients who will receive 40 mg of selinexor as a monotherapy (the "40 mg cohort"). The primary endpoint in the SENTRY-2 Trial is SVR35 at week 24 with a secondary endpoint of TSS50 at week 24. For patients whose SVR does not meet key benchmarks at weeks 12 and 24 compared to baseline, an option to add treatment with a JAKi including ruxolitinib, momelotinib and pacritinib, in addition to selinexor, may be initiated.

The ESSENTIAL Trial

Our evaluation of selinexor to treat myelofibrosis is also supported by data from the ongoing Phase 2 ESSENTIAL trial, an investigator-sponsored open-label, prospective trial evaluating single-agent selinexor at a dose of 80 mg, 60 mg or 40 mg once weekly in adult patients with primary or secondary myelofibrosis with resistance or intolerance to JAKi therapy (the "ESSENTIAL Trial"; NCT03627403). The primary endpoint of the ESSENTIAL Trial is to assess the efficacy of selinexor on SVR. As of August 2024, the data cut-off date, selinexor was administered to 17 patients. Median duration of prior JAKi therapy was 22 months (range 0.5 to 96 months) and 92% (11 of 12) of patients had myelofibrosis refractory to ruxolitinib. The median duration of treatment was 11 months (range 2.8 to 28.8 months). Of the 11 patients who were on treatment for at least 24 weeks, three (27%) patients achieved SVR35 and five (45%) patients achieved SVR of ≥25%. Selinexor treatment led to a reduction in plasma levels of proinflammatory cytokines, especially cytokines regulated by NF-κB activity, consistent with selinexor's proposed mechanism of action. One patient who was initially transfusion dependent became transfusion independent while on study and maintained independence for more than one year. Reduction in marrow reticulin fibrosis from myelofibrosis grade 3 to myelofibrosis grade 1 was observed in a patient who had an assessment at week 72 demonstrating disease modification potential with longer treatment. Median overall survival ("OS") was 35 months (range 2.8 to 54.8 months). This compares favorably with a historical survival of 13 to 14 months in this population. The most common grade ≥3 TEAEs were anemia (24%) and fatigue (24%). These were manageable with treatment interruption and dose reduction, except in one patient who discontinued treatment.

Endometrial Cancer

Overview

Endometrial cancer occurs when cells in the endometrium, which is the inner lining of uterus, begin to grow out of control and invade surrounding tissues. In the U.S., endometrial cancer is the most common gynecological cancer with both incidence and mortality rates continuing to rise. The American Cancer Society (the "ACS") estimates that there will be approximately 62,000 new cases of endometrial cancer diagnosed in 2025 in the U.S. Approximately 16,000 women are expected to be diagnosed with advanced or recurrent endometrial cancer each year in the U.S. with approximately 50% of those patients having *TP53* wild-type endometrial cancer. Endometrial cancer affects mainly post-menopausal women and the average age of women diagnosed with endometrial cancer is 60 years. Endometrial cancer is often detected at an early stage because it frequently produces abnormal vaginal bleeding. Standard of care treatments for patients with endometrial cancer are based on the stage of the disease at diagnosis and the grade of the tumor, and include surgery, radiation therapy, chemotherapy, hormone therapy and targeted therapy. Surgery is the first treatment for almost all women with endometrial cancer, followed by chemotherapy and/or adjuvant radiation therapy for cases of advanced or high grade endometrial cancer. For many patients who respond to adjuvant therapies, the National Comprehensive Cancer Network Clinical Practice Guidelines (the "NCCN Guidelines") recommend a "watch and wait" approach until the disease relapses. Maintenance therapies are designed to prolong the response period and prevent relapse. There are currently no specific targeted FDA approved therapies post-chemotherapy specifically indicated for patients with *TP53* wild-type endometrial cancer. Recently, there has been an increased focus on using molecular classification of endometrial cancers to select the most appropriate therapies for patients. *TP53* wild-type status could represent a potentially unique but fundamental biomarker in endometrial cancer. *TP53* wild-type endometrial cancer co-occurs with both proficient mismatch repair ("pMMR") and deficient mismatch repair ("dMMR") subsets. In 2023 and 2024, dostarlimab-gxly, a new treatment option in combination with chemotherapy, and durvalumab, respectively, were approved by the FDA for patients with dMMR advanced or recurrent endometrial cancer, which represents approximately 20% of the total advanced or recurrent endometrial cancer patient population, and advanced the treatment options for this subgroup. In 2024, both

pembrolizumab and dostarlimab-gxly were approved by the FDA for all patients with advanced or recurrent endometrial cancer irrespective of the MMR status. However, the benefit of such therapies in the pMMR population is not as great compared to the dMMR population, and thus we believe selinexor maintenance therapy can further improve outcomes for patients with pMMR and *TP53* wild-type endometrial cancer, which represent between approximately 40% to 55% of advanced and recurrent endometrial cancer patients.

Clinical correlative and non-clinical mechanism of action studies have shown that inhibition of XPO1 by selinexor leads to the nuclear accumulation and activation of p53, a well-established tumor suppressor protein encoded by the *TP53* gene, resulting in tumor cell senescence and stimulation of the apoptotic pathway leading to cell death.

The EC-042 Trial

In the fourth quarter of 2022, following alignment with the FDA, we initiated a global, Phase 3, randomized, double-blind trial evaluating selinexor as a maintenance-only therapy following systemic therapy in patients with *TP53* wild-type advanced or recurrent endometrial cancer (the "EC-042 Trial"; NCT05611931). Based upon the mechanism of selinexor and the preliminary subgroup data from the SIENDO Trial, discussed below, we believe benefit with selinexor can be observed in all *TP53* wild-type endometrial tumors. The EC-042 Trial was designed to enroll approximately 220 patients whose tumors are *TP53* wild-type and who will be randomized in a 1:1 manner to receive either a 60 mg, once-weekly, administration of oral selinexor or placebo until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint of the EC-042 Trial is progression-free survival ("PFS") as assessed by an investigator and OS as the key secondary endpoint. Further, in connection with the EC-042 Trial, we entered into a global collaboration with Foundation Medicine, Inc. to develop FoundationOne®CDx, a tissue-based next generation sequencing test to identify and enroll patients whose tumors are *TP53* wild-type.

In December 2024, we announced that we were engaged in discussions with the FDA regarding the evolving treatment landscape in advanced or recurrent endometrial cancer, particularly the approval of checkpoint inhibitors (e.g., pembrolizumab, dostarlimab-gxly and durvalumab). The FDA indicated that the EC-042 Trial, which includes a placebo control arm, was not adequately designed to support a marketing application for the proposed indication because it did not account for the current U.S. standard of care, which now includes checkpoint inhibitors in combination with chemotherapy followed by checkpoint inhibitor continuation as maintenance for all patients with advanced or recurrent endometrial cancer, including those with either dMMR tumors (cells that have mutations in certain genes that are involved in correcting mistakes made when DNA is copied in a cell) or pMMR tumors (cells that lack such mutations). Notably, the FDA acknowledged that the magnitude of benefit achieved from checkpoint inhibitors is less for patients with pMMR tumors compared to patients with dMMR tumors. The FDA recommended that we modify the EC-042 Trial to only enroll patients with *TP53* wild-type and pMMR tumors, and redesign the trial to account for the current U.S. treatment landscape. We intend to submit an amendment to the EC-042 Trial protocol to the FDA and other relevant global regulatory authorities incorporating modifications, which we believe are responsive to certain of the FDA's concerns while limiting the length of potential delays and further increased costs that would have been incurred if changes beyond what is described below would have been made.

Specifically, we are modifying the design of the EC-042 Trial to include the following two patient populations for which the primary endpoint of PFS, tested sequentially, and key secondary endpoint of OS will be evaluated: (i) a modified intent to treat population ("mITT") that will include patients whose tumors are *TP53* wild-type and pMMR and also patients whose tumors are *TP53* wild-type and dMMR, but are medically ineligible to receive a checkpoint inhibitor; and (ii) the trial's original intent to treat population ("ITT"), which will include all patients whose tumors are *TP53* wild-type, regardless of MMR status. The mITT population has been defined to take into account certain of the FDA's feedback regarding the evolving treatment options, including checkpoint inhibitors, which show greater efficacy in patients with dMMR tumors compared to pMMR tumors. We are also increasing the trial sample size from 220 patients to approximately 276 patients, to ensure that the mITT population includes approximately 220 patients in order to maintain sufficient power for the primary endpoint of PFS if the FDA chooses to only evaluate PFS in the mITT population. We are continuing to enroll patients in the EC-042 Trial and, depending on the strength of the data, we intend to pursue regulatory approval. However, the FDA may not agree that some, or all, of our proposed modifications to the EC-042 Trial adequately address their concerns. As a result of these proposed modifications, top-line data is expected in mid-2026.

The SIENDO Trial

Our evaluation of selinexor to treat patients with *TP53* wild-type advanced or recurrent endometrial cancer is supported by data from an exploratory subgroup analysis from our SIENDO trial, a multi-center, randomized, double-blinded Phase 3 trial evaluating the efficacy and safety of oral selinexor versus placebo as a front-line maintenance therapy in patients with advanced or recurrent endometrial cancer following at least one prior platinum-based combination chemotherapy treatment (the "SIENDO Trial"; NCT03555422). Participants in the SIENDO Trial with advanced or recurrent disease who had a partial response ("PR") or complete

response (“CR”) after at least 12 weeks of standard of care taxane-platinum combination chemotherapy were randomized in a 2:1 manner to receive either maintenance therapy of 80 mg of selinexor or placebo taken once per week, until disease progression. The primary endpoint in the SIENDO Trial was PFS from time of randomization until death or disease progression as assessed by an investigator.

In the first quarter of 2022, we presented top-line data from the SIENDO Trial, including exploratory subgroup analyses. Selinexor-treated patients had a median PFS of 5.7 months compared to 3.8 months for patients on placebo, representing an improvement of 50%, (eCRF hazard ratio (“HR”) 0.70 (Confidence Interval (“CI”): 0.4993-0.9957), p=0.0486; IRT HR 0.76 (CI: 0.5428-1.0759), p=0.1266) in the full trial population, while patients with *TP53* wild-type advanced or recurrent endometrial cancer treated with selinexor had a median PFS of 13.7 months compared to 3.7 months for patients on placebo. No new safety signals were observed, and there was a discontinuation rate of 10.5% due to adverse events (“AEs”). The most common TEAEs in the SIENDO Trial of any grade were nausea (84%), vomiting (52%), constipation (37%) and thrombocytopenia (37%). The most common grade 3 TEAEs were nausea (10%), neutropenia (9%), thrombocytopenia (7%) and asthenia (6%).

In June 2024, we presented updated long-term safety and efficacy data from the pre-specified exploratory subgroup analysis from our SIENDO Trial in patients with advanced or recurrent *TP53* wild-type endometrial cancer at the American Society of Clinical Oncology Annual Meeting. In the exploratory subgroup analysis, 113 patients with *TP53* wild-type advanced or recurrent endometrial cancer were randomized to receive selinexor (n=77) or placebo (n=36) as maintenance therapy after first-line platinum-based chemotherapy. As of the April 1, 2024 data cut-off date, and a median duration of follow-up of 36.8 months, selinexor-treated patients had a median PFS of 28.4 months compared to 5.2 months for patients receiving placebo (HR 0.44; 95% CI 0.27–0.73). In the selinexor-treated patients with *TP53* wild-type and pMMR and *TP53* wild-type and dMMR endometrial cancer, median PFS was 39.5 months and 13.1 months, respectively, compared to 4.9 months and 3.7 months, respectively. The updated analyses also highlighted findings from a quality-adjusted time without symptoms or toxicity analysis (“Q-TWiST”) used to assess quality and toxicity-adjusted PFS. The findings showed the restricted mean Q-TWiST for selinexor to be 26 months compared to 15 months for placebo, resulting in a difference of nearly 11 months. No new safety signals were identified as of the April 1, 2024 data cut-off date. The most common TEAEs in selinexor treated *TP53* wild-type patients were nausea (90%), vomiting (60%), and diarrhea (45%), the majority of which were grades 1-2. The most common reported grade 3-4 TEAEs included neutropenia (20%), nausea (13%), and thrombocytopenia (10%). TEAEs leading to discontinuations in the selinexor group were reported in 17% of patients.

Multiple Myeloma

Overview

Multiple myeloma is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin, also known as M protein, in the serum or urine, bone destruction, kidney disease and immunodeficiency. Multiple myeloma is the second most common blood cancer in the world and there is currently no cure. The ACS estimates that nearly 36,000 new cases of multiple myeloma will be diagnosed in the U.S. in 2025. Myeloma occurs most commonly in people over age 65 and the risk of developing multiple myeloma increases with age.

The treatment of multiple myeloma has improved over the last 20 years due to the use of high-dose chemotherapy and autologous stem cell transplantation, which is often restricted to healthier, often younger patients. Treatment decisions are based on physician and patient choice rather than clear treatment guidelines, with the current standard of care being to switch drug classes once a regimen stops working. In addition to our XPO1 inhibitor, a number of non-chemotherapy drugs such as PIs, IMiDs, mAbs, bispecific antibodies, and chimeric antigen receptor T-cell (“CAR-T”) therapy, have also emerged as treatment options within the last two decades. The introduction of these non-chemotherapeutic novel agents has led to a significant increase in the survival of patients with multiple myeloma. However, despite the wide variety of newly approved or experimental therapies that are being used to treat patients with relapsed or refractory multiple myeloma either alone or in combination, nearly all patients will eventually succumb to their disease. With approximately 12,500 deaths from multiple myeloma in the U.S. alone estimated for 2025 according to the ACS, we believe that there remains a need for therapies for patients whose disease has relapsed after, or is refractory to, available therapy or for whom current therapy is not suitable.

XPOVIO is currently approved to treat multiple myeloma in adult patients who have received at least one prior therapy based on data from the BOSTON Trial and in adult patients with penta-refractory multiple myeloma based on data from the STORM Trial.

The BOSTON Trial

The December 2020 FDA approval of XPOVIO in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy was based on the results of the BOSTON Trial, a multi-center, Phase 3, randomized trial conducted at over 150 clinical sites internationally. The BOSTON Trial evaluated 402 adult patients

with relapsed or refractory multiple myeloma who had received one to three prior lines of therapy. The trial was designed to compare the efficacy and safety of once-weekly oral selinexor in combination with once-weekly administration of Velcade® (bortezomib) plus low-dose dexamethasone (the "XVd Arm") versus twice-weekly administration of Velcade® plus dexamethasone (the "Vd Arm"). The primary endpoint of the BOSTON Trial was PFS and key secondary endpoints included overall response rate ("ORR") and the rate of peripheral neuropathy, among others. Additionally, the BOSTON Trial allowed for patients on the Vd Arm to crossover to the XVd Arm following objective (quantitative) progression of disease verified by an Independent Review Committee.

Despite the trial having a high proportion of patients with high-risk cytogenetics (approximately 50%), the median PFS in the XVd Arm was 13.9 months compared to 9.5 months in the Vd Arm, representing a 4.4 month (47%) increase in median PFS (HR of 0.70; p=0.0075). The XVd Arm also demonstrated a significantly greater ORR compared to the Vd Arm (76.4% vs. 62.3%, p=0.0012).

Further, XVd therapy demonstrated a significantly higher rate of deep responses, defined as ≥ very good partial response compared to Vd therapy (44.6% vs. 32.4%) as well as a longer median duration of response ("DOR") (20.3 months vs. 12.9 months). Additionally, 17% of patients on the XVd arm achieved a CR or a stringent CR as compared to 10% of patients receiving Vd therapy. All responses were confirmed by an Independent Review Committee. Rates of peripheral neuropathy were significantly lower for patients receiving XVd therapy compared to those receiving Vd therapy (32% vs. 47%). In addition, peripheral neuropathy rates ≥ grade 2 were also significantly lower in the XVd Arm compared to the Vd Arm (21% vs. 34%).

The most common adverse reactions (≥20%) in patients who received XVd were fatigue (59%), nausea (50%), decreased appetite (35%), diarrhea (32%), peripheral neuropathy (32%), upper respiratory tract infection (29%), decreased weight (26%), cataract (22%) and vomiting (21%). Grade 3-4 laboratory abnormalities (≥10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia. In the BOSTON Trial, fatal adverse reactions occurred in 6% of patients within 30 days of last treatment. Serious adverse reactions occurred in 52% of patients who received XVd. Treatment discontinuation rate due to adverse reactions was 19%.

In June 2023, we presented data from an unplanned subgroup analysis of BOSTON patients without prior PI exposure (XVd: n = 47; Vd: n= 48) at the 2023 European Hematology Association Hybrid Congress, which analysis demonstrated an approximate tripling of median PFS for XVd compared to Vd at 29.5 vs 9.7 months; HR for PFS favored XVd at 0.29 (95% CI 0.14 - 0.63, nominal p=<0.001). This data was published in the European Journal of Hematology in August 2024.

The STORM Trial

The July 2019 FDA approval of XPOVIO in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 mAb was based on the results of the STORM Trial. This indication was approved under accelerated approval. As the BOSTON Trial served as the confirmatory trial for the accelerated approval of XPOVIO based on the STORM Trial, the BOSTON supplemental New Drug Application approval in December 2020 fulfilled the requirement of an accelerated approval.

The STORM Trial was a global, multi-center, single-arm Phase 2b clinical trial evaluating oral selinexor in combination with standard, low-dose dexamethasone ("Xd") in patients with heavily pretreated relapsed or refractory multiple myeloma. These heavily pretreated patients had a median of seven prior therapeutic regimens, including a median of 10 unique anti-myeloma agents. Specifically, the myeloma patients who were eligible for the trial had prior treatment with the two PIs, Velcade® and Kyprolis® (carfilzomib), the two IMiDs, Revlimid® (lenalidomide) and Pomalyst®(pomalidomide), and the anti-CD38 mAb Darzalex® (daratumumab), as well as alkylating agents, and their disease was refractory to glucocorticoids, at least one PI, at least one IMiD, Darzalex®, and their most recent therapy. In all patients, this myeloma was considered "triple-class refractory."

The FDA's accelerated approval of XPOVIO was based upon the efficacy and safety in a pre-specified subgroup analysis of the 83 patients in the STORM Trial with documented penta-refractory myeloma, as the benefit-risk ratio appeared to be greater in this more heavily pre-treated population than in the overall trial population. In addition to multiple-refractory disease, patients in the STORM Trial had rapidly progressing myeloma, with a median 22% increase in disease burden in the 12 days from screening to initial therapy. The ORR in this patient population was 25.3%.

For the STORM Trial's primary endpoint, selinexor achieved an ORR of 26%, including two (2%) stringent CRs, six (5%) very good partial responses, and 24 (20%) PRs and the trial therefore met its primary endpoint. Both patients who had relapsed after CAR-T therapy achieved PRs. Minimal response per International Myeloma Working Group criteria was observed in 16 (13%) patients and 48 (39%) patients had stable disease. Median time to PR or better was 4.1 weeks. The clinical benefit rate, meaning a minimal response or better, was 39%. All responses were adjudicated by an Independent Review Committee consisting of four independent experts in the treatment of multiple myeloma.

Median DOR was 4.4 months. PFS was 3.7 months and OS was 8.6 months. In the 39% of patients who achieved a minimal response or better, median OS was 15.6 months, compared to a median OS of 1.7 months in patients whose disease progressed or where response was not evaluable.

The most common adverse reactions (≥20%) in patients who received Xd were thrombocytopenia (74%), fatigue (73%), nausea (72%), anemia (59%), decreased appetite (53%), decreased weight (47%), diarrhea (44%), vomiting (41%), hyponatremia (39%), neutropenia (34%), leukopenia (28%), constipation (25%), dyspnea (24%) and upper respiratory tract infection (21%). In the STORM Trial, fatal adverse reactions occurred in 9% of patients. Serious adverse reactions occurred in 58% of patients. Treatment discontinuation rate due to adverse reactions was 27%.

The XPORT-MM-031/EMN29 Trial

The EMN29 trial is an ongoing randomized global Phase 3 trial sponsored by the European Myeloma Network evaluating selinexor in combination with pomalidomide and dexamethasone ("SPd") versus elotuzumab, pomalidomide, and dexamethasone ("EloPd") in patients with relapsed or refractory multiple myeloma (the "EMN29 Trial"; NCT05028348). The EMN29 Trial is designed to evaluate a 40 mg once weekly dose of selinexor compared to standard dosing of elotuzumab in combination with pomalidomide and dexamethasone in relapsed or refractory multiple myeloma as the immediate next line of therapy after treatment with anti-CD38 antibodies. Patients enrolled in the EMN29 Trial received one to four prior lines of therapy, including a PI and lenalidomide, and had an anti-CD38 mAb in their most recent prior line of therapy. The primary endpoint of the EMN29 Trial is PFS, with ORR, OS and DOR, among others, as secondary endpoints.

The determination to initiate the EMN29 Trial was based on data from an all-oral arm of the Phase 1b/2 STOMP Trial (the "STOMP Trial"; NCT02343042) and the Phase 2 Trial XPORT-MM-028 (the "MM-028 Trial"; NCT04414475) in which selinexor was evaluated in combination with pomalidomide and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma who received at least two prior lines of therapy, including a PI and an IMiD.

During the second half of 2024, we amended certain aspects of the design for the EMN29 Trial, including a reduction in the number of patients that are targeted for enrollment from 222 patients to approximately 120 patients and revisions to the trial's statistical plan and powering assumptions. These changes were made as a result of slower than expected patient enrollment due to the intense competitive environment and based on updated clinical data on the SPd regimen from the STOMP and MM-028 Trials, which showed a median PFS of 18.4 months for SPd 40 mg, as published in the Frontiers of Oncology Journal in May 2024. We believe that, depending on the strength of the data, the EMN29 Trial may still serve as the basis for a registration; however, there is increased risk to approvability given that the reduction in the number of enrolled patients.

The STOMP Trial: Arm 12 (selinexor in combination with mezigdomide and dexamethasone)

In October 2023, we entered into a clinical trial collaboration and supply agreement with Bristol-Myers Squibb Company ("BMS") to evaluate mezigdomide, BMS' proprietary investigational cereblon E3 ligase modulator (CELMoD™) agent, in combination with selinexor in patients with relapsed or refractory multiple myeloma progressing after T-cell immunotherapies. This additional arm of the STOMP Phase 1b/2 trial is evaluating mezigdomide in combination with selinexor doses of either 40 mg or 60 mg once weekly plus dexamethasone in patients who have prior exposure to IMiDs, PIs, and anti-CD38 mAb treatment. All patients must have received at least two prior lines of therapy, and either have progressed after or are not eligible to receive CAR-T or bispecific antibody treatment. The primary endpoints of this trial are to assess the ORR and the clinical benefit rate. Key secondary endpoints include PFS, OS and DOR. In addition, the trial will evaluate dynamic changes in T-cell populations and activity as patients undergo treatment. Under the terms of the agreement with BMS, we are sponsoring the trial as a new arm of the STOMP Trial and BMS will supply the trial's clinical drug mezigdomide. The trial is currently enrolling patients in the Phase 1b portion.

Diffuse Large B-Cell Lymphoma

Overview

DLBCL is the most common type of Non-Hodgkin's lymphoma, a cancer that starts in cells called lymphocytes, which are part of the body's immune system. Lymphocytes are found in the lymph nodes and other lymphoid tissues, such as the spleen and bone marrow, as well as in the blood. According to the Lymphoma Research Foundation, over 18,000 people are diagnosed with DLBCL annually in the U.S. Although DLBCL can occur at any age, the median age at diagnosis is approximately 66 years of age. Approximately two-thirds of all newly diagnosed patients are cured using front-line chemotherapy (typically "R-CHOP"). Poor outcomes for patients who failed a R-CHOP regimen prompted efforts to discover new treatment approaches for DLBCL, both up-front and at the time of relapse. Despite the availability of CAR-T therapy, many patients with relapsed or refractory DLBCL are not medically stable enough to undergo this type of treatment. In addition, various other targets have been studied in the treatment of DLBCL but may also not be well tolerated in heavily pretreated patients.

The SADAL Trial

In June 2020, the FDA approved XPOVIO under accelerated approval as a single-agent oral treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. This approval was based on the results of the SADAL Trial, an open-label Phase 2b clinical trial evaluating single-agent oral selinexor (60 mg, twice weekly) in patients that had relapsed or refractory DLBCL after at least two prior multi-agent therapies and who were ineligible for transplantation, including high dose chemotherapy with stem cell rescue. In this population, selinexor demonstrated an ORR of 29%, including a CR rate of 13%. Responses were seen in all subgroups evaluated regardless of age, gender, prior therapy, DLBCL subtype or prior stem cell transplant therapy. Patient responses were durable with a median DOR of 9.3 months (23.0 months for patients who achieved a CR). Importantly, responses were associated with longer survival, underscoring the potential of oral XPO1 inhibition as an oral, non-chemotherapeutic option for patients with relapsed or refractory DLBCL. Part 2 of the SADAL Trial (the "KCP-330-009 Trial"; NCT02227251) is ongoing to evaluate alternate dosing (40 mg, twice weekly; 60 mg twice weekly for cycles 1 and 2; and 60 mg weekly for subsequent cycles).

The most common adverse reactions (≥20%) in patients who received selinexor were fatigue (63%), nausea (57%), diarrhea (37%), decreased appetite (37%), decreased weight (30%), constipation (29%), vomiting (28%), and pyrexia (22%). Grade 3-4 laboratory abnormalities (≥15%) were thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia. In the SADAL Trial, fatal adverse reactions occurred in 3.7% of patients within 30 days of last treatment. Serious adverse reactions occurred in 46% of patients who received selinexor. Treatment discontinuation rate due to adverse reactions was 17%.

The XPORT-DLBCL-030 Trial

The XPORT-DLBCL-030 trial, which is intended to serve as the confirmatory trial to the accelerated approval of XPOVIO in DLBCL granted by the FDA in June 2020, is a Phase 2/3 multi-center, randomized trial evaluating the combination of selinexor and rituximab, gemcitabine and dexamethasone ("R-GDP") in patients with relapsed or refractory DLBCL (the "XPORT-DLBCL-030 Trial"; NCT04442022). The Phase 2 portion of the trial is evaluating efficacy, safety and tolerability of R-GDP plus either selinexor 40 mg or 60 mg. The Phase 3 portion of the trial is currently designed to evaluate the selected dose (as identified in the Phase 2 trial) of selinexor or matching placebo given with the standard combination immunochemotherapy R-GDP to patients with at least one prior therapy and who are not intended for stem cell transplant and CAR-T cell therapy. The primary endpoint of the Phase 3 portion of the XPORT-DLBCL-030 Trial would be PFS. The XPORT-DLBCL-030 Trial is currently in the Phase 2 portion of the evaluation and is recruiting.

OUR ELTANEXOR PROGRAM

Myelodysplastic Neoplasms

Overview

Myelodysplastic neoplasms ("MDS") are a group of hematologic malignancies whereby the bone marrow does not make enough healthy blood cells (white blood cells, red blood cells, and platelets). Hypomethylating agents ("HMAs") are the current standard of care for patients newly diagnosed with high-risk MDS. There is currently no other class of therapy approved for relapsed or refractory MDS patients; the current standard of care is participation in a clinical trial or best supportive care, such as transfusions and symptomatic treatment for cytopenias. Our product candidate, eltanexor, is a novel, oral SINE compound that, like selinexor, selectively blocks the nuclear export protein XPO1. Based on the data described below, we have observed single-agent clinical activity of eltanexor to treat patients with HMA-refractory MDS.

In January 2022, the FDA granted Orphan Drug Designation for eltanexor for the treatment of MDS. In addition, in July 2022, the FDA granted Fast Track designation for eltanexor as monotherapy for the treatment of patients with relapsed or refractory intermediate, high-, or very high-risk MDS and the European Commission adopted the Committee for Orphan Medicinal Products opinion to designate eltanexor as an orphan medicinal product for the treatment of MDS in the European Union ("EU").

The KCP-8602-801 Trial

In September 2021, we initiated a Phase 2 expansion trial of an ongoing open-label Phase 1/2 trial investigating eltanexor as a single-agent or in combination with approved and investigational agents in patients with several types of hematologic and solid tumor cancers (the "KCP-8602-801 Trial"; NCT02649790). The KCP-8602-801 Trial is designed to evaluate eltanexor monotherapy in 83 patients with HMA-refractory, intermediate or high-risk MDS. The primary endpoint for this Phase 2 expansion trial is ORR with PFS and OS, among others, as secondary endpoints. In May 2023, we announced interim data from the Phase 2 portion of the KCP-8602-801 Trial at the 17th International Congress of Myelodysplastic Syndromes. As of the February 8, 2023 data cut-off date, 30 patients had been treated with 10 mg of oral eltanexor on Days 1-5 of each week. Eltanexor demonstrated a 27% ORR in the ITT population and a 31% ORR in the efficacy evaluable population, with ORR consisting of marrow CR and hematologic improvement only. No PRs or CRs were observed. Median OS was 8.7 months in both populations. Transfusion independence rate for red blood cells and/or platelets was 29%. Eltanexor was generally well-tolerated and manageable. The most common AEs were asthenia (47%), diarrhea (43%), and nausea (33%), the majority of which were grades 1-2. The most common grade ≥3 TEAEs were neutropenia (30%), thrombocytopenia (26.7%), and asthenia (16.7%).

As announced in January 2024, further clinical development of our eltanexor program continues to remain on hold in an effort to focus our resources on our prioritized late-stage programs.

OTHER PIPELINE PROGRAMS

In addition to selinexor, we also may advance other novel drug candidates, such as KPT-9274. KPT-9274 is our first-in-class dual inhibitor of p21-activated kinase 4 ("PAK4") and nicotinamide phosphoribosyltransferase ("NAMPT"). Co-inhibition of PAK4 and NAMPT may lead to synergistic anti-tumor effects through energy depletion, inhibition of DNA repair, cell cycle arrest, inhibition of proliferation, and ultimately apoptosis. Normal cells are more resistant to inhibition by KPT-9274 due in part to their relative genomic stability and lower metabolic rates. Hematologic and solid tumor cells that have become dependent on both PAK4 and NAMPT pathways may be susceptible to single-agent cytotoxicity of KPT-9274.

KPT-9274 has shown broad evidence of anti-cancer activity against hematological and solid tumor malignant cells while showing minimal toxicity to normal cells in vitro. In mouse xenograft studies, oral KPT-9274 has shown evidence of anti-cancer activity and tolerability. To our knowledge, we are the only company with an allosteric PAK4 modulator and/or NAMPT specific inhibitor currently in clinical development. We are evaluating development opportunities for KPT-9274.

Collaboration, License and Other Strategic Agreements

We have formed, and intend to continue to form, strategic alliances to develop and commercialize our products and product candidates. We enter into collaborations when there is a strategic advantage to us and we believe the financial terms of the collaboration are favorable for meeting our short- and long-term strategic objectives. Currently, we maintain complete development and commercial rights to our products and product candidates in the U.S. and Japan and have entered into the following key agreements:

Menarini

In December 2021, we entered into a license agreement with the Menarini Group ("Menarini"), an Italian pharmaceutical company (the "Original Menarini Agreement"). Pursuant to the Original Menarini Agreement, we granted Menarini a non-exclusive license to develop, and an exclusive license to commercialize, products containing selinexor (the "Product") for all human oncology indications in the European Economic Area, UK, Switzerland, Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Uzbekistan, Ukraine, Turkey, Mexico, all Central America countries and all South America countries (collectively, the "Menarini Territory"). In March 2023, the Original Menarini Agreement was amended (the "Amended Menarini Agreement") to expand the Menarini Territory to include all countries in the continent of Africa and Saudi Arabia, United Arab Emirates, Kuwait, Oman, Qatar, Bahrain, Lebanon, Jordan, Iraq and Yemen (together with the Menarini Territory, the "Expanded Menarini Territory"). In addition, we granted to Menarini a non-exclusive license to package and label the Product in or outside of the Expanded Menarini Territory for all human oncology indications solely to enable Menarini to commercialize the Product within the Expanded Menarini Territory.

We received an upfront cash payment of $75.0 million in December 2021 and $3.5 million in April 2023 upon execution of the Original Menarini Agreement and the Amended Menarini Agreement, respectively. In addition, we are entitled to receive additional milestone payments from Menarini if certain development and sales performance milestones are achieved in the future. We are also eligible to receive tiered royalties ranging from the mid-teens to mid-twenties based on future net sales of the Product in the Expanded Menarini Territory. The payments owed by Menarini to us are subject to reduction in specified circumstances. Menarini will reimburse us for 25% of all expenses we incur for the development of the Product during 2022 through 2025, provided that such reimbursements shall not exceed $15.0 million per calendar year.

Antengene

In May 2020, we entered into an amendment of our May 2018 license agreement with Antengene Therapeutics Limited ("Antengene") (the "Original Antengene Agreement", and, as amended, the "Amended Antengene Agreement"). Antengene is a corporation organized and existing under the laws of Hong Kong, and a subsidiary of Antengene Corporation Co. Ltd., a corporation organized and existing under the laws of the People's Republic of China. Under the terms of the Amended Antengene Agreement, Antengene has the exclusive rights to develop and commercialize, at its own cost, selinexor, eltanexor, KPT-9274, each for the diagnosis, treatment and/or prevention of all human oncology indications, and verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam, Australia and New Zealand (the "Antengene Territory"). In August 2023, Antengene entered into an exclusive arrangement with a Hong Kong pharmaceutical company for the commercialization of selinexor in mainland China.

Under the terms of the Original Antengene Agreement, we received an upfront cash payment of $11.7 million in 2018. In June 2020, we received an additional $11.7 million upfront payment upon execution of the Amended Antengene Agreement. In addition, we are entitled to receive additional milestone payments from Antengene if certain other regulatory and commercialization goals are achieved in the future. We are also eligible to receive tiered double-digit royalties based on future net sales of selinexor and eltanexor, and tiered single- to double-digit royalties based on future net sales of verdinexor and KPT-9274 in the Antengene Territory.

FORUS

In December 2020, we entered into an exclusive distribution agreement for the commercialization of XPOVIO in Canada with FORUS Therapeutics Inc. ("FORUS"), a Canadian biopharmaceutical company. Under the terms of the agreement, we received an upfront payment of $5.0 million in December 2020 and are eligible to receive additional payments if certain prespecified regulatory and commercial milestones are achieved by FORUS. We are also eligible to receive double-digit royalties on future net sales of XPOVIO in Canada. FORUS received the exclusive rights to commercialize XPOVIO in Canada and is responsible for all regulatory filings and obligations required for registering XPOVIO. We have retained the exclusive production rights and will supply finished product to FORUS for commercial use in Canada.

Promedico

In February 2020, we entered into an exclusive distribution agreement with Promedico Ltd. ("Promedico") for the commercialization of XPOVIO in Israel, the West Bank, Gaza Strip and the territories under control of the Palestinian Authority (the "Promedico Territory"). We will receive certain prespecified payments and are eligible to receive additional payments if certain regulatory and commercial milestones are achieved by Promedico. We are also eligible to receive double-digit royalties on future net sales in the Promedico Territory. Promedico received the exclusive rights to commercialize XPOVIO in the Promedico Territory and is responsible for all regulatory filings and obligations required for registering XPOVIO. We have retained exclusive production rights and will supply finished product for commercial use in the Promedico Territory.

Other

In addition to the above agreements, we have other collaborations related to the development or commercialization of our products and product candidates, such as the Cooperative Research and Development Agreement with the National Cancer Institute's Cancer Therapy Evaluation Program and a clinical trial collaboration and supply agreement with BMS, as discussed above, to collaborate with us on studies to investigate the safety and efficacy of selinexor in various oncology indications; the European Myeloma Network, with which we have a collaboration, as discussed above; and arrangements with academic and private non-academic institutions, which conduct investigator-sponsored clinical trials in a variety of hematological and solid tumor malignancies.

In July 2021, we entered into a license agreement with Libo Pharma Corp. ("Libo") under which we granted to Libo an exclusive license to manufacture, develop and commercialize Interleukin 12 products in certain countries in Asia, Africa and Oceania.

In December 2023, we amended the license agreement to include global development and commercialization rights for all indications except for acute radiation syndrome. We received from Libo an upfront payment and a milestone payment upon completion of technology transfer and are entitled to receive development and regulatory milestones and single-digit royalties on future net sales of KPT-1200.

In addition, in February 2024 we reacquired KPT-350 and other assets, which we had sold to Biogen Inc. ("Biogen") in January 2018 under an asset purchase agreement that was subsequently terminated by Biogen in June 2022. KPT-350 is a clinical stage SINE compound under evaluation for neurological indications, including amyotrophic lateral sclerosis. We intend to evaluate KPT-350 for development internally or through a third-party collaborator or licensor.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our products and product candidates, our core technologies, and other know-how, to operate without infringing on the proprietary rights of others and to prevent others from infringing our proprietary or intellectual property rights. Our policy is to seek to protect our proprietary and intellectual property position by, among other methods, filing patent applications in the U.S. and in foreign jurisdictions related to our proprietary technology and products and product candidates. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position.

We file patent applications directed to the composition of matter and methods of use and manufacture for our products and product candidates. As of February 14, 2025, we were the sole owner of 48 patents in the U.S. and we had 13 pending patent applications in the U.S., two pending international applications filed under the Patent Cooperation Treaty ("PCT"), 178 granted patents and 92 pending patent applications in foreign jurisdictions. The PCT is an international patent law treaty that provides a unified procedure for filing a single initial patent application to seek patent protection for an invention simultaneously in each of the member states. Although a PCT application is not itself examined and cannot issue as a patent, it allows the applicant to seek protection in any of the member states through national-phase applications.

The intellectual property portfolios for our key products and product candidates as of February 14, 2025 are summarized below.

- **Selinexor (KPT-330)**: Our selinexor patent portfolio covers: the composition of matter of selinexor; various polymorphic forms of selinexor, including the polymorph used in selinexor's commercial drug substance; various methods of use of selinexor; as well as methods of making selinexor. There are two U.S. patents covering selinexor's composition of matter. One of the patents will expire in July 2032 and the other will expire in July 2033 in view of Patent Term Extension awarded by the U.S. Patent and Trademark Office ("USPTO"). The U.S. patents covering the polymorph used in selinexor's commercial drug substance will expire in August 2035. Any other patents that may issue in the U.S. as part of our selinexor patent portfolio will expire no earlier than July 2032. Any patents that may issue in foreign jurisdictions will likewise expire no earlier than 2032.
- **Supplementary Protection Certificates:** We have filed applications for Supplementary Protection Certificates ("SPCs") based on European Patent No. 2,736,887 directed to the composition of matter and use of selinexor. Some applications have granted and others are pending.
- **Eltanexor** (**KPT-8602)**: Our eltanexor patent portfolio covers both the composition of matter and methods of making and using eltanexor, and consists of four issued U.S. patents, three pending non-provisional U.S. patent applications, 29 issued foreign patents and 16 pending foreign patent applications. Any patents that may issue in the U.S. as part of our eltanexor patent portfolio will expire no earlier than 2034, not including any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in foreign jurisdictions will likewise expire no earlier than 2034.
- **PAK4/NAMPT Inhibitors**: Our PAK4/NAMPT inhibitors patent portfolio covers both the composition of matter and methods of use of the PAK4/NAMPT inhibitors described therein, such as KPT-9274, and consists of five patent families with seven issued U.S. patents, 25 issued foreign patents, one pending U.S. non-provisional patent application, and three pending foreign patent applications in total. Any patents that may issue in the U.S. based on the pending U.S. non-provisional application will expire in 2034, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents that may issue based on the pending foreign patent applications will likewise expire in 2034. Foreign patent applications covering the composition of matter and methods of use of KPT-9274 have been filed in 22 countries/regions.
- **Biomarkers for XPO1 Inhibitors**: Our patent portfolio also covers biomarkers related to treatment with XPO1 inhibitors, such as selinexor, and consists of one pending non-provisional U.S. patent application, one pending PCT application and six pending foreign patent applications. Any patents that may issue in the U.S. based on the pending U.S.

non-provisional application will expire in 2040, absent any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in foreign jurisdictions will likewise expire in 2040. Any patents that may issue in the U.S. or foreign jurisdictions based on the pending PCT application will expire no earlier than 2044, not including any terminal disclaimer, patent term adjustment due to administrative delays by the USPTO or patent term extension under the Hatch-Waxman Act. Any patents issued in foreign jurisdictions will likewise expire in 2044.

In addition to the patent portfolios covering our key products and product candidates, as of February 14, 2025, our patent portfolio also includes 5 patents in the U.S. and 16 granted foreign patents and pending patent applications in the U.S. and foreign jurisdictions relating to other XPO1 inhibitors and their use in targeted therapeutics and combination therapies for XPO1 inhibitors.

In the U.S., we have trademark registrations for KARYOPHARM, KARYOPHARM THERAPEUTICS, our color logo, our logo in greyscale, KARYOPHARM THERAPEUTICS with the color logo, XPOVIO, PORE for our online research portal, and KARYFORWARD and our KARYFORWARD logo for our financial aid and charitable services. Outside of the U.S., XPOVIO is registered or pending in 46 additional jurisdictions, and is registered in Katakana in Japan, Hangul in South Korea, and Chinese characters in Taiwan. KARYOPHARM, the greyscale logo, KARYOPHARM THERAPEUTICS with the color logo, and the KARYFORWARD logo are each registered in four jurisdictions outside of the U.S. We also have registrations or applications for eight additional possible product names in numerous foreign jurisdictions.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the U.S., the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the U.S., a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. See "*Government Regulation - Patent Term Restoration and Extension*" below for additional information on such extensions. We have filed applications for patent term extension in the U.S., Korea, Taiwan, Australia and China based on the granted patent in each jurisdiction directed to the composition of matter of selinexor. In the U.S., Korea and Taiwan we have been awarded 342 days, 150 days and 5 years, respectively, of patent term extension. In Australia, the term of the patent has been extended from July 26, 2032 to March 8, 2037 and in China we are awaiting a determination from the relevant authority. There is no assurance that we will benefit from any patent term extension. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each product candidate and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our products and product candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, patent applications that we may file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Our issued patents and any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us. In addition, because of the extensive time required for clinical development and regulatory review of a product candidate we may develop, it is possible that, before any of our product candidates 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.

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, scientific advisors, employees and consultants, and invention assignment agreements with our employees. We also have agreements with selected consultants, scientific advisors and collaborators requiring assignment of inventions. The confidentiality agreements are designed to protect our proprietary information and, in the case of agreements or clauses requiring invention assignment, to grant us ownership of technologies that are developed through our relationship with a third party.

With respect to our proprietary drug discovery and optimization platform, we consider trade secrets and know-how to be our primary intellectual property. Trade secrets and know-how can be difficult to protect. We anticipate that with respect to this technology platform, these trade secrets and know-how may over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, knowledge, experience and scientific resources provide us with certain competitive advantages, we face competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are numerous companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. We are aware of several other XPO1 inhibitors in clinical development world-wide. For example, in June 2020, Menarini acquired Stemline Therapeutics, Inc., including its oral XPO1 inhibitor, felezonexor. Felezonexor, currently in Phase 1b, is in clinical trials as a potential treatment for patients with advanced solid tumors. Additionally, in August 2022, Shanghai Junshi Biosciences Co., Ltd announced FDA approval of its investigational new drug application ("IND") for JS110, an XPO1 inhibitor in development in various blood and solid tumors.

Many of the companies against which we or our collaborators currently compete or which we may compete with in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, marketing approved products and achieving ex-U.S. positive coverage/reimbursement decisions than we or our collaborators do. Mergers and acquisitions in the pharmaceutical and biotechnology 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 or our collaborators in recruiting and retaining qualified scientific, commercial 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.

The key competitive factors affecting the success of any approved oncology drug product, including our products and product candidates, if approved, are likely to be their actual or perceived efficacy, safety, tolerability, convenience and price, the availability of alternative cancer therapies and the availability of reimbursement from government and other third-party payors. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products, or commercialize existing products in new indications, and those products are or are perceived to be safer, more effective, more convenient, less expensive or more tolerable than any products that we have or may develop. Our competitors also may obtain FDA or other regulatory approval 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.

In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic drugs. Generic drugs for the treatment of cancer are on the market and additional products are expected to become available on a generic basis over the coming years. If we obtain marketing approval for our product candidates or for XPOVIO in other indications, we expect that they will be priced at a significant premium over generic versions of older chemotherapy agents and other cancer therapies.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. There are numerous available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our products and product candidates may compete with many existing drugs and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates will be complimentary with them. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved products are well-established therapies and are widely accepted by physicians, patients and third-party payors.

In addition to currently marketed therapies, there are also a number of products in late-stage clinical development to treat cancer. These products in development may provide efficacy, safety, tolerability, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may represent significant competition for any of our products or product candidates for which we obtain marketing approval.

XPOVIO competes with and, if approved, our product candidates may compete with, currently marketed products and/or investigational therapies as discussed below.

Myelofibrosis

The current standard of care for patients with myelofibrosis who are not candidates for allogeneic HSCT, which is currently the only treatment for myelofibrosis that can provide a clinical cure, is to treat the patients with JAKi's, the only currently approved drug therapy for treatment for myelofibrosis to reduce spleen volume and improve symptoms. There are only four JAKi's currently approved, including ruxolitinib, fedratinib, pacritinib and momelotinib.

In addition, there are a number of product candidates in late-stage development, some of which could receive approval earlier than selinexor (e.g., pelabresib). Ongoing clinical trials, such as those involving imetelstat, bomedemstat, navtemadlin, siremadlin, and zilurgisertib are studying the treatment of myelofibrosis either with JAKi therapy, non-JAKi therapy or a combination of JAKi and drug treatment.

Endometrial Cancer

The treatment landscape for endometrial cancer has undergone considerable change since 2023. Surgery continues to be the first treatment for almost all women with endometrial cancer. For cases of advanced or high-grade endometrial cancer, or upon disease progression, several combination therapies have become available. These therapies include the use of checkpoint inhibitors (e.g., pembrolizumab, dostarlimab-gxly and durvalumab) in combination with chemotherapy followed by checkpoint inhibitor maintenance therapy as well as checkpoint inhibitor (pembrolizumab) in combination with a tyrosine kinase inhibitor (lenvatinib).

Multiple Myeloma

Many therapies are approved for use in patients with multiple myeloma in the U.S., Europe and other parts of the world. Although XPOVIO is the only XPO1 inhibitor that has received marketing approval, we compete with multiple other treatment types in our approved indications. The primary competitors of XPOVIO in multiple myeloma include those that currently treat patients ranging from newly diagnosed patients to those with relapsed or refractory multiple myeloma and are indicated for use either as single agent and/or as combination therapies. The current standard of care for the treatment of relapsed or refractory multiple myeloma includes IMiDs (e.g., thalidomide, lenalidomide, pomalidomide), PIs (e.g., bortezomib, carfilzomib, ixazomib), monoclonal antibodies (e.g., daratumamab, isatuximab, elotuzumab), B-cell maturation antigens, including CAR-Ts (e.g., idecabtagene vicleucel, ciltacabtagene autoleucel) and bispecific antibodies. New classes/types of therapies are being introduced to the market each year. For example, TECVAYLI® (teclistamab-cqyv), the first bispecific T-Cell engager, was approved by the FDA in October 2022, followed by approvals of two more bispecifics, ELREXFIO™ (elranatamab-bcmm) and TALVEY® (talquetamab-tgvs) in August 2023. Other T-cell engaging therapies, bispecifics with different targets, and immunomodulators are in clinical development and may be introduced into the multiple myeloma market in 2025 and beyond. CARVYKTI® (ciltacabtagene autoleucel; cilta-cel) and Abecma® (idecabtagene vicleucel; ide-cel) were approved in April 2024 for the treatment of multiple myeloma in earlier lines. In addition, new competitors and label expansions into earlier lines of existing therapies could also be approved in the future (e.g. belantamab mafodotin and linvoseltamab).

DLBCL

The initial therapy for DLBCL typically consists of multi-agent cytotoxic drugs in combination with the mAb rituximab (or a rituximab biosimilar). In patients with DLBCL who are not elderly and who have good organ function, high dose chemotherapy with stem cell transplantation is often used at first relapse. Over the past five years, a number of therapeutic interventions have been approved in the U.S., Europe and other parts of the world for the treatment of patients with relapsed or refractory DLBCL who have received at least two prior therapies and/or are not eligible for ASCT/HSCT. In addition, certain currently approved therapeutic interventions are also being evaluated in late-stage development in earlier lines of therapy for the treatment of patients with DLBCL, such as CD19-directed CAR-T therapies (e.g., axicabtagene ciloleucel), CD79b-directed antibody-drug conjugates (e.g., polatuzumab vedotin-piiq) and CD19-directed cytolytic antibody (e.g., tafasitamab-cxix and loncastuximab), and anti-CD20/CD3 bispecifics (e.g., glofitamab, and epcoritamab, odronextomab).

Other agents are listed in the NCCN Guidelines and/or the European Society for Medical Oncology guidelines for use after one to two prior therapies, although they have not been formally approved by the FDA for treatment of DLBCL, including: lenalidomide, ibrutinib, and generic multiagent chemotherapy, including gemcitabine, oxaliplatin, and bendamustine.

In addition, a number of anti-cancer agents are in mid to late-stage development for the treatment of patients with DLBCL, including bispecific antibodies (e.g., mosunetuzumab), antibody drug conjugates (e.g., brentuximab vedotin), small molecules (e.g., enzastaurin, acalabrutinib, and zanubrutinib) and monoclonal antibodies (e.g., zilovertamab).

Sales and Marketing

Following the July 2019 U.S. commercial launch of XPOVIO in multiple myeloma and subsequent FDA approvals in 2020 in both earlier stage multiple myeloma and DLBCL, our commercial team has focused its efforts on educating health care providers on the efficacy and safety profile of XPOVIO with the goal of enabling cancer patients access to this important treatment. We are commercializing XPOVIO in the U.S. with our own focused, customer-facing teams, including sales specialists, reimbursement and access support specialists, and nurse liaisons, each typically with years of experience in hematology/oncology. We have approximately 60 field-based employees in the U.S. who call on academic and community-based healthcare professionals who treat multiple myeloma and DLBCL, as well as our reimbursement team. We believe that the current size of our sales force is appropriate at this time to effectively reach our target audience in the specialty markets in which we currently operate. Continued growth of our current marketed products and the launch of any future products may require further expansion of our field force and support organization within and outside of the U.S. For the foreseeable future, we intend to develop and commercialize XPOVIO and our product candidates alone in the U.S. and expect to rely on partners to develop and commercialize our products in territories outside of the U.S. In executing our strategy, our goal is to retain oversight over the global development and commercialization of our products by playing an active role in their commercialization or finding partners who share our vision, values, and culture.

Our sales force is supported by an experienced sales leadership team and professionals in marketing, reimbursement and market access, market research and analytics, commercial operations, finance and human resources. Our sales and marketing organization uses a variety of pharmaceutical marketing strategies to promote XPOVIO, including sales calls, peer-to-peer education, non-personal promotional, and digital content. We employ third-party vendors, such as advertising agencies, market research firms and suppliers of marketing and other sales support-related services, to assist with our commercial activities.

Our patient support program, KaryForward®, is dedicated to providing assistance and resources to our patients with multiple myeloma and DLBCL and their caregivers throughout their XPOVIO treatment. KaryForward® offers support in navigating insurance coverage issues and processes and enabling continuation of our patients' ability to access XPOVIO in the case of delays or interruptions in the insurance process. We also offer a copay card, which offers eligible commercial patients who have insurance to receive their prescription for as little as $5.00 per prescription. Further, the KaryForward® program assists eligible patients who do not have insurance or lack coverage to be able to access XPOVIO treatment through our Patient Assistance Program. Under our KaryForward® program, patients are assigned a dedicated nurse case manager, who serves as a point of contact to help patients and their caregivers navigate the treatment process, including by explaining prescription instructions, providing psychosocial support and additional nonclinical education regarding XPOVIO, highlighting expectations when taking XPOVIO and providing referrals for additional third-party support, such as transportation assistance.

Manufacturing

We do not own or operate, and have no plans to establish, any manufacturing facilities for our products or product candidates. We currently rely, and expect to continue to rely, on third-party contract manufacturers to manufacture our products and product candidates for our commercial and clinical use.

The clinical and commercial supplies of the drug product for XPOVIO are currently manufactured pursuant to a combination of long-term supply agreements and as-needed purchase order agreements with our third-party manufacturers.

Selinexor is a small molecule drug and is manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry and formulation processes of selinexor have been developed to meet our large-scale manufacturing needs and do not require unusual equipment in the manufacturing process. We generally maintain sufficient inventory levels throughout our supply chain to exceed our two-year forecasts for XPOVIO in order to minimize the risks of supply disruption.

To support the commercialization and development of our products and product candidates, we have developed a fully integrated manufacturing support system, including scientific oversight, quality assurance, quality control, regulatory affairs and inventory control policies and procedures. These support systems are intended to enable us to maintain high standards of quality for our products. We intend to continue to outsource the manufacture and distribution of our products for the foreseeable future, and we believe this manufacturing strategy will enable us to direct more of our financial resources to the commercialization and development of our products and product candidates.

Government Regulation

Government authorities in the U.S., at the federal, state and local level, and in other countries and jurisdictions, including the EU, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, pricing, reimbursement, sales, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the U.S. and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources. The regulatory requirements applicable to drug product development, approval and marketing are subject to change, and regulations and administrative guidance often are revised or reinterpreted by the agencies in ways that may have a significant impact on our business.

Review and Approval of Drugs in the U.S.

In the U.S., the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act (the "FDCA") and implementing regulations. A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products, and for their regulatory approval, is typically referred to as a sponsor. The failure of a sponsor to comply with applicable requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject a sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

The FDA must approve our product candidates for therapeutic indications before they may be marketed in the U.S. A sponsor seeking approval to market and distribute a new drug in the U.S. generally must satisfactorily complete each of the following steps before the product candidate will be approved by the FDA:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice ("GLP") regulations, as applicable;
- design of a clinical protocol and submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board ("IRB") representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices ("GCP") to establish the safety and effectiveness of the proposed drug product for each indication;
- preparation and submission to the FDA of a new drug application ("NDA") requesting marketing approval for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product in clinical development and proposed labelling;
- review and evaluation of the data on the product candidate by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current good manufacturing practices ("cGMP") requirements and to assure that the chemistry, manufacturing and controls ("CMC") are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees pursuant to the Prescription Drug User Fee Act ("PDUFA");
- approval of an NDA for the new drug product authorizing marketing for particular indications in the U.S.; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies ("REMS") and post-approval studies required by the FDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards and the U.S. Department of Agriculture's Animal Welfare Act, if applicable. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND.

Some long-term preclinical testing, such as animal tests of reproductive AEs and carcinogenicity, may be required to be included in a marketing application. With passage of the FDA's Modernization Act 2.0 in December 2022, Congress eliminated provisions in both the FDCA and the Public Health Service Act ("PHSA") that required animal testing in support of an NDA or a biologics license application ("BLA"). While animal testing may still be conducted, the FDA was authorized to rely on alternative non-clinical tests, including cell-based assays, microphysiological systems, or bioprinted or computer models.

In addition, sponsors usually must also develop additional information about the chemistry and physical characteristics of the investigational product and 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 candidate product and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the candidate product does not undergo unacceptable deterioration over its shelf life.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. An IND must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA or BLA. In support of a request for an IND, a sponsor must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. Beyond reviewing an IND to assure the safety and rights of patients, the FDA's review also focuses on the quality of the investigation and whether it will be adequate to permit an evaluation of the drug's effectiveness and safety and of the biological product's safety, purity and potency. An initial IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial may proceed. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical trial or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a partial clinical hold might state that a specific protocol or part of a protocol may not proceed, while other parts of a protocol or other protocols may do so. No more than 30 days after the imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor with a written explanation of the basis for the hold. Following the issuance of a clinical hold or partial clinical hold, a clinical trial may only resume once the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed or recommence. Occasionally, clinical holds are imposed due to manufacturing issues that may present safety issues for the clinical trial subjects.

Once an IND application takes effect, the sponsor of the IND may amend the application as needed to ensure that the clinical trials are conducted according to protocols included in the IND. The FDA has indicated that sponsors are expected to submit amendments for new protocols or changes to existing protocols before implementation of the respective changes. New studies may begin, however, when the sponsor has submitted the change to the FDA for its review and the new protocol or changes to the existing protocol have been approved by the IRB with the responsibility for review and approval of the studies. In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct a continuing review and reapprove the trial at least annually. The IRB must review and approve, among other things, the trial protocol and informed consent information to be provided to trial subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by a Data Monitoring Committee, an independent group of qualified experts organized by the trial sponsor. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the trial. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Clinical Studies Outside the U.S. in Support of FDA Approval

In connection with our clinical development program, we may have trial sites outside the U.S. When a foreign clinical trial site operates as part of a global clinical trial that is under an IND, all IND requirements must be met unless waived for that foreign clinical trial site. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the trial complies with certain regulatory requirements of the FDA in order to use the trial as support for an IND or application for marketing approval. Specifically, the studies must be conducted in accordance with GCP, including undergoing review and receiving approval by an independent ethics committee and seeking and receiving informed consent from subjects. GCP requirements encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

The acceptance by the FDA of trial data from clinical trials conducted outside the U.S. in support of U.S. approval may be subject to certain conditions or may not be accepted at all. In cases where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the U.S., the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the U.S. population and U.S. medical practice; (ii) the trials were performed by clinical investigators of recognized competence and pursuant to GCP regulations; and (iii) the data may be considered valid without the need for an on-site inspection by the FDA, or if the FDA considers such inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means.

In addition, even where the foreign trial data are not intended to serve as the sole basis for approval, the FDA will not accept the data as support for an application for marketing approval unless the trial is well-designed and well-conducted in accordance with GCP requirements and the FDA is able to validate the data from the trial through an onsite inspection if deemed necessary. Many foreign regulatory authorities have similar approval requirements. In addition, such foreign trials are subject to the applicable local laws of the foreign jurisdictions where the trials are conducted.

Reporting Clinical Trial Results

Under the PHSA, sponsors of clinical trials of certain FDA-regulated products, including prescription drugs and biologics, are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the U.S. National Institutes of Health (the "NIH"). In particular, information related to the product, patient population, phase of investigation, trial sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Although sponsors are also obligated to disclose the results of their clinical trials after completion, disclosure of the results can be delayed in some cases for up to two years after the date of completion of the trial. The NIH's Final Rule on registration and reporting requirements for clinical trials became effective in 2017.

The PHSA grants the Secretary of Health and Human Services the authority to issue a notice of noncompliance to a responsible party for failure to submit clinical trial information as required. The responsible party, however, is allowed 30 days to correct the noncompliance and submit the required information. As of December 19, 2024, the FDA has issued six notices of non-compliance, thereby signaling the government's willingness to begin enforcing these requirements against non-compliant clinical trial sponsors. While these notices of non-compliance did not result in civil monetary penalties, the failure to submit clinical trial information to clinicaltrials.gov is a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues. Violations may also result in injunctions and/or criminal prosecution or disqualification from federal grants.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of IND products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or treatment IND Application.

There is no obligation for a sponsor to make its investigational products available for expanded access; however, as required by amendments to the FDCA included in the 21st Century Cures Act (the "Cures Act"), passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests with respect to product candidates in development to treat serious diseases or conditions, it must make that policy publicly available. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 trial for a covered investigational product; or 15 days after the investigational product receives designation from the FDA as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, in May 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain IND products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written trial protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol, and any subsequent material amendment to the protocol, must be submitted to the FDA as part of the IND, and progress reports detailing the status of the clinical trials must be submitted to the FDA annually.

Human clinical trials are typically conducted in four sequential phases, which may overlap or be combined:

Phase 1: The drug is initially introduced into a small number of healthy human subjects or patients with the target disease (e.g., cancer) or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product. These clinical trials are commonly referred to as "pivotal" studies, which denotes a trial that presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug.

Phase 4: Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

A clinical trial may combine the elements of more than one phase and the FDA often requires more than one Phase 3 trial to support marketing approval of a product candidate. A company's designation of a clinical trial as being of a particular phase is not necessarily indicative that the trial will be sufficient to satisfy the FDA requirements of that phase because this determination cannot be made until the protocol and data have been submitted to and reviewed by the FDA. Moreover, as noted above, a pivotal trial is a clinical trial that is believed to satisfy FDA requirements for the evaluation of a product candidate's safety and effectiveness such that it can be used, alone or with other pivotal or non-pivotal trials, to support regulatory approval. Generally, pivotal trials are Phase 3

trials, but they may be Phase 2 trials if they are adequate and well-controlled studies to establish the evidence needed for regulatory approval.

In March 2022, the FDA released final guidance entitled "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics," which outlines how developers can utilize an adaptive trial design commonly referred to as a seamless trial design in early stages of oncology biological product development (e.g., the first-in-human clinical trial) to compress the traditional three phases of trials into one continuous trial called an expansion cohort trial. Information to support the design of individual expansion cohorts are included in IND applications and assessed by the FDA. Expansion cohort trials can potentially bring efficiency to biological product development and reduce developmental costs and time.

In December 2022, with the passage of the Food and Drug Omnibus Reform Act ("FDORA"), Congress required sponsors to develop and submit a diversity action plan for each Phase 3 clinical trial or any other "pivotal trial" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, action plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans. In June 2024, as mandated by FDORA, the FDA issued draft guidance outlining the general requirements for diversity action plans ("DAPs"). Unlike most guidance documents issued by the FDA, the DAP guidance when finalized will have the force of law because FDORA specifically dictates that the form and manner for submission of DAPs are specified in FDA guidance.

In June 2023, the FDA issued draft guidance with updated recommendations for GCPs aimed at modernizing the design and conduct of clinical trials. The updates are intended to help pave the way for more efficient clinical trials to facilitate the development of medical products. The draft guidance was adopted from the International Council for Harmonisation's recently updated E6(R3) draft guideline that was developed to enable the incorporation of rapidly developing technological and methodological innovations into the clinical trial enterprise. In addition, the FDA issued draft guidance outlining recommendations for the implementation of decentralized clinical trials.

Interactions with FDA During the Clinical Development Program

Following the clearance of an initial IND and the commencement of clinical trials, the sponsor will continue to have interactions with the FDA. Progress reports detailing the results of clinical trials must be submitted annually within 60 days of the anniversary dates that the IND went into effect and more frequently if serious adverse events occur. These reports must include a development safety update report. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the occurrence of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

In addition, sponsors are given opportunities to meet with the FDA at certain points in the clinical development program. Specifically, sponsors may meet with the FDA prior to the submission of an IND (Pre-IND meeting), at the end of Phase 1 clinical trial (EOP1 meeting), at the end of Phase 2 clinical trial (EOP2 meeting) and before an NDA or BLA is submitted (Pre-NDA or Pre-BLA meeting). Meetings at other times may also be requested. There are five types of meetings that occur between sponsors and the FDA. Type A meetings are those that are necessary for an otherwise stalled product development program to proceed or to address an important safety issue. Type B meetings include pre-IND and pre-NDA/pre-BLA meetings, as well as end of phase meetings such as EOP2 meetings. A Type C meeting is any meeting other than a Type A or Type B meeting regarding the development and review of a product, including, for example, meetings to facilitate early consultations on the use of a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use. A Type D meeting is focused on a narrow set of issues and is limited to no more than two focused topics and should not require input from more than three disciplines or divisions. Finally, INTERACT meetings are intended for novel products and development programs that present unique challenges in the early development of an investigational product.

These meetings provide an opportunity for the sponsor to share information about the data gathered to date with the FDA and for the FDA to provide advice on the next phase of development. For example, at an EOP2 meeting, a sponsor may discuss its Phase 2 clinical results and present its plans for the pivotal Phase 3 clinical trial(s) that it believes will support the approval of the new product. Such meetings may be conducted in person, via teleconference/videoconference or written response only with minutes reflecting the questions that the sponsor posed to the FDA and the agency's responses. The FDA has indicated that its responses, as conveyed in meeting minutes and advice letters, only constitute mere recommendations and/or advice made to a sponsor and, as such, sponsors are

not bound by such recommendations and/or advice. Nonetheless, from a practical perspective, a sponsor's failure to follow the FDA's recommendations for design of a clinical program may put the program at significant risk of failure. In September 2023, the FDA issued draft guidance outlining the terms of such meetings in more detail.

FDA approval of companion diagnostics

In August 2014, the FDA issued final guidance clarifying the requirements that apply to the approval of therapeutic products and in vitro companion diagnostics. According to the guidance, for novel drugs, a companion diagnostic device and its corresponding therapeutic should be approved or cleared contemporaneously by the FDA for the use indicated in the therapeutic product's labeling. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. In July 2016, the FDA issued a draft guidance intended to assist sponsors of the drug therapeutic and in vitro companion diagnostic device on issues related to co-development of the products.

The 2014 guidance also explains that a companion diagnostic device used to make treatment decisions in clinical trials of a biologic product candidate generally will be considered an investigational device, unless it is employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, the diagnostic device generally will be considered a significant risk device under the FDA's Investigational Device Exemption ("IDE") regulations. Thus, the sponsor of the diagnostic device will be required to comply with the IDE regulations. According to the guidance, if a diagnostic device and a product are to be studied together to support their respective approvals, both products can be studied in the same investigational trial, if the trial meets both the requirements of the IDE regulations and the IND regulations. The guidance provides that depending on the details of the trial plan and subjects, a sponsor may seek to submit an IND alone, or both an IND and an IDE.

In April 2020, the FDA issued additional final guidance that describes considerations for the development and labeling of companion diagnostic devices to support the indicated uses of multiple drug or biological oncology products, when appropriate. This guidance builds upon existing policy regarding the labeling of companion diagnostics. In its 2014 guidance, the FDA stated that if evidence is sufficient to conclude that the companion diagnostic is appropriate for use with a specific group of therapeutic products, the companion diagnostic's intended use or indications for use should name the specific group of therapeutic products, rather than specific products. The 2020 guidance expands on the policy statement in the 2014 guidance by recommending that companion diagnostic developers consider a number of factors when determining whether their test could be developed, or the labeling for approved companion diagnostics could be revised through a supplement, to support a broader labeling claim such as use with a specific group of oncology therapeutic products (rather than listing an individual therapeutic product(s)). Subsequently, in June 2023, the FDA issued another final guidance to describe the FDA's voluntary pilot program for certain oncology drug products used with certain in vitro diagnostic tests.

Under the FDCA, in vitro diagnostics, including companion diagnostics, are regulated as medical devices. In the U.S., the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import and post-market surveillance. Unless an exemption applies, diagnostic tests require pre-notification marketing clearance or approval from the FDA prior to commercial distribution.

The FDA previously has required in vitro companion diagnostics intended to select the patients who will respond to the product candidate to obtain pre-market approval ("PMA") simultaneously with approval of the therapeutic product candidate. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the sponsor must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee. For federal fiscal year 2025, the standard fee is $540,783 and the small business fee is $135,196.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the Quality System Regulation, which covers the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging, and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the U.S.

Manufacturing and Other Regulatory Requirements

Concurrently with clinical trials, sponsors usually complete additional animal safety studies, develop additional information about the chemistry and physical characteristics of the product candidate and finalize a process for manufacturing commercial quantities of the product candidate in accordance with cGMP requirements. Specifically, the FDA's regulations require that pharmaceutical products be manufactured in approved facilities and in accordance with cGMPs. The cGMP regulations include requirements relating to organization of personnel, buildings and facilities, equipment, control of components and product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports and returned or salvaged products. Manufacturers and other entities involved in the manufacture and distribution of approved pharmaceuticals are required to register their establishments with the FDA and some state agencies, and they are subject to periodic unannounced inspections by the FDA for compliance with cGMPs and other requirements. Both domestic and foreign manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether foreign or domestic, is deemed misbranded under the FDCA.

Inspections must follow a "risk-based schedule" that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated. Changes to the manufacturing process, specifications or container closure system for an approved product are strictly regulated and often require prior FDA approval before being implemented. The FDA's regulations also require, among other things, the investigation and correction of any deviations from cGMP and the imposition of reporting and documentation requirements upon the sponsor and any third-party manufacturers involved in producing the approved product. The PREVENT Pandemics Act, which was enacted in December 2022, clarifies that foreign drug manufacturing establishments are subject to registration and listing requirements even if a drug undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the U.S. prior to being imported or offered for import into the U.S.

Pediatric Studies

Under the Pediatric Research Equity Act (the "PREA") applications and certain types of supplements to applications must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor must submit an initial Pediatric Study Plan ("PSP") within 60 days of an EOP2 meeting or as may be agreed between the sponsor and the FDA. Those plans must contain an outline of the proposed pediatric study or studies the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The sponsor and the FDA must reach agreement on a final plan. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs. The statute also directs the FDA, in consultation with the National Cancer Institute, members of the internal committee established under section 505C of the FDCA and the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee, to establish, publish, and regularly update a list of molecular targets considered, on the basis of data the FDA determines to be adequate, to be substantially relevant to the growth or progression of a pediatric cancer, and that may trigger PREA requirements.

The FDA may, on its own initiative or at the request of the sponsor, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The FDA is required to send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under the PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation.

Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation intended for a non-cancer indication, although the FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA by announcing that it does not intend to grant any additional Orphan Drug Designations for rare pediatric subpopulations of what is otherwise a common disease. Further, Section 505B of the FDCA, as amended by FDARA, requires that any original NDA or BLA submitted on or after August 18, 2020, for a new active ingredient, must contain reports on the molecularly targeted pediatric cancer investigation, unless the requirement is waived or deferred, if the drug that is the subject of the application is: (i) intended for the treatment of an adult cancer, and (ii) directed at a molecular target that the Secretary of HHS determines to be substantially relevant to the growth or progression of a pediatric cancer in accordance with FDA guidance. The FDA maintains a list

of diseases that are exempt from PREA requirements due to low prevalence of disease in the pediatric population. In May 2023, the FDA issued draft guidance that further describes the pediatric study requirements under PREA.

Fast Track, Breakthrough Therapy, Priority Review and Regenerative Advanced Therapy Designations

The FDA is authorized to designate certain products for expedited development and review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as Fast Track designation, Breakthrough Therapy designation, Priority Review designation and Regenerative Advanced Therapy designation. None of these expedited programs change the standards for approval but they may help expedite the development or approval process of product candidates.

Specifically, the FDA may grant a product Fast Track designation if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Second, a product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Finally, with passage of the Cures Act in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy (as defined in the Cures Act) that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality ("IMM") and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

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. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, an additional post-approval confirmatory study(ies) to verify and describe the drug's clinical benefit or, in certain cases where the clinical endpoint takes longer to mature, the completion of the study. As a result, a drug candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

In December 2022, Congress modified certain provisions governing accelerated approval of drug products. Specifically, the new legislation authorized the FDA to require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded and to submit progress reports on its post-approval studies to the FDA every six months until the study is completed. Moreover, FDORA established expedited procedures authorizing the FDA to withdraw an accelerated approval if certain conditions are met, including where a required confirmatory study fails to verify and describe the predicted clinical benefit or where evidence demonstrates the product is not shown to be safe or effective under the conditions of use. The FDA may also use such procedures to withdraw an accelerated approval if a sponsor fails to conduct any required post-approval trial of the product with due diligence, including with respect to "conditions specified by the Secretary." The new procedures include the provision of due notice and an explanation for a proposed withdrawal, and opportunities for a meeting with the Commissioner or the Commissioner's designee and a written appeal, among other things.

In March 2023, the FDA issued draft guidance that outlines its current thinking and approach to accelerated approval. The agency indicated that the accelerated approval pathway is commonly used for approval of oncology drugs due to the serious and life-threatening nature of cancer. Although single-arm trials have been commonly used to support accelerated approval, a randomized controlled trial is the preferred approach as it provides a more robust efficacy and safety assessment and allows for direct comparisons to an available therapy. To that end, the FDA outlined considerations for designing, conducting, and analyzing data for trials intended to support accelerated approvals of oncology therapeutics. While this guidance is currently only in draft form and will ultimately not be legally binding even when finalized, sponsors typically observe the FDA's guidance closely to ensure that their investigational products qualify for accelerated approval. Subsequently, in December 2024, the FDA issued additional draft guidance relating to accelerated approval. These guidances describe the FDA's latest thinking on what it means to conduct a confirmatory trial with due diligence and how the FDA plans to interpret whether such a study needs to be underway at the time of approval. While these guidances are currently only in draft form and will ultimately not be legally binding even when finalized, sponsors typically observe the FDA's guidance closely to ensure that their investigational products qualify for accelerated approval.

Filing and Review of NDAs

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, along with information relating to the product's chemistry, manufacturing, controls, safety updates, patent information, abuse information and proposed labeling, are submitted to the FDA as part of an application requesting approval to market the product candidate for one or more indications. Data may come from company-sponsored clinical trials intended to test the safety and effectiveness of a product's use 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 a drug product.

The fee required for the submission and review of an application under the Prescription Drug User Fee Act (the "PDUFA"), is substantial (for example, for federal fiscal year 2025 this application fee is $4,310,002) and the sponsor of an approved application is

also subject to an annual program fee, currently set at $403,889 per eligible prescription product. These fees are typically adjusted annually, and exemptions and waivers may be available under certain circumstances, such as where a waiver is necessary to protect the public health, where the fee would present a significant barrier to innovation, or where the sponsor is a small business submitting its first human therapeutic application for review. The standard review time for an initial NDA or BLA is 12 months and it is ten months for a supplemental application.

Specifically, the FDA conducts a preliminary review of all applications within 60 days of receipt and must inform the sponsor at that time or before whether an application is sufficiently complete to permit substantive review. In pertinent part, the FDA's regulations state that an application "shall not be considered as filed until all pertinent information and data have been received" by the FDA. In the event that FDA determines that an application does not satisfy this standard, it will issue a Refuse to File ("RTF") determination to the sponsor. Typically, a RTF will be based on administrative incompleteness, such as clear omission of information or sections of required information; scientific incompleteness, such as omission of critical data, information or analyses needed to evaluate safety and effectiveness or provide adequate directions for use; or inadequate content, presentation, or organization of information such that substantive and meaningful review is precluded. The FDA may request additional information rather than accept an application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing.

After the submission is accepted for filing, the FDA begins an in-depth substantive review of the application. The FDA reviews the application to determine, among other things, whether the proposed product is safe and effective for its intended use, whether it has an acceptable purity profile and whether the product is being manufactured in accordance with cGMP. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months from the filing date in which to complete its initial review of a standard application that is a new molecular entity, and six months from the filing date for an application with "priority review." The review process may be extended by the FDA for three additional months to consider new information or in the case of a clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission. Despite these review goals, it is not uncommon for FDA review of an application to extend beyond the PDUFA goal date.

In connection with its review of an application, the FDA will typically submit information requests to the sponsor and set deadlines for responses thereto. The FDA will also conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether the manufacturing processes and facilities comply with cGMPs. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and are adequate to assure consistent production of the product within required specifications. The FDA also may inspect the sponsor and one or more clinical trial sites to assure compliance with IND and GCP requirements and the integrity of the clinical data submitted to the FDA. To ensure cGMP and GCP compliance by its employees and third-party contractors, a sponsor may incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

Moreover, the FDA will review a sponsor's financial relationship with the principal investigators who conducted the clinical trials in support of the NDA. That is because, under certain circumstances, principal investigators at a clinical trial site may also serve as scientific advisors or consultants to a sponsor and receive compensation in connection with such services. Depending on the level of that compensation and any other financial interest a principal investigator may have in a sponsor, the sponsor may be required to report these relationships to the FDA. The FDA will then evaluate that financial relationship and determine whether it creates a conflict of interest or otherwise affects the interpretation of the trial or the integrity of the data generated at the principal investigator's clinical trial site. If so, the FDA may exclude data from the clinical trial site in connection with its determination of safety and efficacy of the investigational product.

Additionally, the FDA may refer an application, including applications for novel product candidates which present difficult questions of safety or efficacy, to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations when making final decisions on approval. Data from clinical trials are not always conclusive, and the FDA or its advisory committee may interpret data differently than the sponsor interprets the same data. The FDA may also re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the sponsor during the review process.

The FDA also may require submission of a REMS if it determines that a REMS is necessary to ensure that the benefits of the product outweigh its risks and to assure the safe use of the product. The REMS could include medication guides, physician communication plans, assessment plans and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools. The FDA determines the requirement for a REMS, as well as the specific REMS provisions, on a case-by-case basis. If the FDA concludes a REMS is needed, the sponsor of the application must submit a proposed REMS and the FDA will not approve the application without a REMS.

Decisions on NDAs

The FDA reviews a sponsor's NDA to determine, among other things, whether the product is safe and whether it is effective for its intended use(s), with the latter determination being made on the basis of substantial evidence. The term "substantial evidence" is defined under the FDCA as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the product involved, on the basis of which it could fairly and responsibly be concluded by such experts that the product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

The FDA has interpreted this evidentiary standard to require at least two adequate and well-controlled clinical trials to establish effectiveness of a new product. Under certain circumstances, however, the FDA has indicated that a single trial with certain characteristics and additional information may satisfy this standard. This approach was subsequently endorsed by Congress in 1998 with legislation providing, in pertinent part, that "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical trial and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the FDA may consider such data and evidence to constitute substantial evidence." This modification to the law recognized the potential for the FDA to find that one adequate and well-controlled clinical trial with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness. In December 2019, the FDA issued draft guidance further explaining the studies that are needed to establish substantial evidence of effectiveness. Although the FDA has not yet finalized that guidance, it did issue additional draft guidance in September 2023 that outlines considerations for relying on confirmatory evidence in lieu of a second clinical trial.

After evaluating the application and all related information, including the advisory committee recommendations, if any, and inspection reports of manufacturing facilities and clinical trial sites, the FDA will issue either a Complete Response Letter ("CRL") or an approval letter. To reach this determination, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. This "benefit-risk" assessment is informed by the extensive body of evidence about the product's safety and effectiveness in the NDA. This assessment is also informed by other factors, including: the severity of the underlying condition and how well patients' medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the post-market setting; and whether risk management tools are necessary to manage specific risks. In connection with this assessment, the FDA review team will assemble all individual reviews and other documents into an "action package," which becomes the record for FDA review. The review team then issues a recommendation, and a senior FDA official makes a decision.

A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. The CRL may require additional clinical or other data, additional pivotal Phase 3 clinical trial(s) and/or other significant and time- consuming requirements related to clinical trials, preclinical studies or manufacturing. If a CRL is issued, the sponsor will have one year to respond to the deficiencies identified by the FDA, at which time the FDA can deem the application withdrawn or, in its discretion, grant the sponsor an additional six-month extension to respond. The FDA has committed to reviewing resubmissions in response to an issued CRL in either two or six months depending on the type of information included. Even with the submission of this additional information, however, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. The FDA has taken the position that a CRL is not final agency action making the determination subject to judicial review. The FDA has indicated that sponsors may request a formal hearing on the CRL or they may file a request for reconsideration or a request for a formal dispute resolution.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific indications. That is, the approval will be limited to the conditions of use (e.g., patient population, indication) described in the FDA-approved labeling. Further, depending on the specific risk(s) to be addressed, the FDA may require that contraindications, warnings or precautions be included in the product labeling, require that post-approval trials, including Phase 4 clinical trials, be conducted to further assess a product's safety after approval, require testing and surveillance programs to monitor the product after commercialization or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further

marketing of a product based on the results of post-marketing trials or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Under the Ensuring Innovation Act, which was signed into law in April 2021, the FDA must publish action packages summarizing its decisions to approve new drugs within 30 days of approval of such products. To date, CRLs are not publicly available documents.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including AEs of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug or biologic.

It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. Moreover, with passage of the Pre-Approval Information Exchange Act in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Previously, such communications were permitted under FDA guidance but the new legislation explicitly provides protection to sponsors who convey certain information about products in development to payors, including unapproved uses of approved products. In addition, in October 2023, the FDA published draft guidance outlining the agency's non-binding policies governing the distribution of scientific information on unapproved uses to healthcare providers. This draft guidance calls for such communications to be truthful,

non-misleading, factual, and unbiased and include all information necessary for healthcare providers to interpret the strengths and weaknesses and validity and utility of the information about the unapproved use. This guidance was finalized by the FDA on January 6, 2025.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services ("HHS"), as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products is subject to a variety of federal and state laws. The Prescription Drug Marketing Act (the "PDMA") was the first federal law to set minimum standards for the registration and regulation of drug distributors by the states and to regulate the distribution of drug samples. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution. In November 2013, the federal Drug Supply Chain Security Act (the "DSCSA") became effective in the U.S., mandating an industry-wide, electronic, interoperable system to trace prescription drugs through the pharmaceutical distribution supply chain with a ten-year phase-in process. Manufacturers were required by November 2023 to have such systems and processes. So as not to disrupt supply chains, the FDA has granted certain exemptions from enhanced drug distribution security requirements for eligible trading partners for particular periods of time.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the sponsor to rely, in part, on the FDA's previous findings of safety and effectiveness for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the sponsor for approval of the application "were not conducted by or for the sponsor and for which the sponsor has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and efficacy data that were not developed by the sponsor. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the Section 505(b)(2) sponsor can establish that reliance on the FDA's previous approval is scientifically appropriate, the sponsor may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) sponsor.

Generic Drugs and Regulatory Exclusivity

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, a sponsor must submit an abbreviated new drug application ("ANDA") to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug ("RLD").

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug..."

Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication Approved Drug Products with Therapeutic Equivalence Evaluations, also referred to as the Orange Book. Clinicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing clinicians or patient.

Under the Hatch-Waxman Act, the FDA may not approve an ANDA or 505(b)(2) application until any applicable period of regulatory exclusivity for the RLD has expired. The FDCA provides a period of five years of regulatory exclusivity for a new drug containing a new chemical entity ("NCE"). For the purposes of this provision, the FDA has consistently taken the position that an NCE is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. This interpretation was confirmed with the enactment of the Ensuring Innovation Act in April 2021. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, a generic or follow-on drug application may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the sponsor may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical trials, other than bioavailability or bioequivalence studies, that were conducted by or for the sponsor and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical trial is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight months for a drug that has three or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The new legislation also authorizes the FDA to expedite review of competitor generic therapies or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

Hatch-Waxman Patent Certification and the 30-Month Stay

As part of the submission of an NDA or certain supplemental applications, NDA sponsors are required to list with the FDA each patent with claims that cover the sponsor's product or an approved method of using the product. Upon approval of a new drug, each of the patents listed in the application for the drug is then published in the Orange Book. The FDA's regulations governing patent listings were largely codified into law with the enactment of the Orange Book Modernization Act in January 2021. When an ANDA sponsor files its application with the FDA, the sponsor is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA sponsor is not seeking approval. To the extent that the Section 505(b)(2) sponsor is relying on studies conducted for an already approved product, the sponsor is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA sponsor would.

Specifically, the sponsor must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the sponsor does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the ANDA sponsor is not seeking approval).

If the ANDA sponsor has provided a Paragraph IV certification to the FDA, the sponsor must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent

infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA sponsor.

To the extent that the Section 505(b)(2) sponsor is relying on studies conducted for an already approved product, the sponsor is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA sponsor would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of an NCE, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) sponsor.

Orphan Drug Designation and Exclusivity

Orphan Drug Designation in the U.S. is designed to encourage sponsors to develop products intended for treatment of rare diseases or conditions. In the U.S., a rare disease or condition is statutorily defined as a condition that affects fewer than 200,000 individuals in the U.S. or that affects more than 200,000 individuals in the U.S. and for which there is no reasonable expectation that the cost of developing and making available the product for the disease or condition will be recovered from sales of the product in the U.S.

Orphan Drug Designation qualifies a company for tax credits and potentially market exclusivity for seven years following the date of the product's approval if granted by the FDA. An application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. A product becomes an orphan when it receives Orphan Drug Designation from the Office of Orphan Products Development at the FDA based on acceptable confidential requests. The product must then go through the review and approval process like any other product.

A sponsor may request Orphan Drug Designation of a previously unapproved product or new orphan indication for an already marketed product. In addition, a sponsor of a product that is otherwise the same product as an already approved orphan drug may seek and obtain Orphan Drug Designation for the subsequent product for the same rare disease or condition if it can present a plausible hypothesis that its product may be clinically superior to the first approved product. More than one sponsor may receive Orphan Drug Designation for the same product for the same rare disease or condition, but each sponsor seeking Orphan Drug Designation must file a complete request for designation.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same product for the same disease or condition for seven years, except in certain limited circumstances. If a product designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

The period of market exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the disease or condition for which the product has been designated. Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if the company with orphan drug exclusivity is not able to meet market demand or the subsequent product is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan drug exclusivity regardless of a showing of clinical superiority. Under Omnibus legislation signed by President Trump in December 2020, the requirement for a product to show clinical superiority applies to drug products that received Orphan Drug Designation before enactment of amendments to the FDCA in 2017 but have not yet been approved by FDA.

In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of market exclusivity, the term "same disease or condition" in the statute means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved.

Pediatric Exclusivity

Pediatric exclusivity is a type of non-patent marketing exclusivity in the U.S. and, if granted, provides for the attachment of an additional six months of exclusivity. For drug products, the six-month exclusivity may be attached to the term of any existing patent or regulatory exclusivity, including the orphan exclusivity and regulatory exclusivities available under the Hatch-Waxman provisions of the FDCA. For biologic products, the six-month period may be attached to any existing regulatory exclusivities but not to any patent terms. The conditions for pediatric exclusivity include the FDA's determination that information relating to the use of a new product in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric clinical trials, and the sponsor agreeing to perform, and reporting on, the requested clinical trials within the statutory timeframe. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patents that cover the product are extended by six months. Although this is not a patent term extension, it effectively extends the regulatory period during which the FDA cannot approve another application.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted is typically 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 ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Healthcare Compliance

In the U.S., biopharmaceutical manufacturers and their products are subject to extensive regulation at the federal and state level, such as laws intended to prevent fraud and abuse in the healthcare industry. Healthcare providers and third-party payors play a primary role in the recommendation and prescription of pharmaceutical products that are granted marketing approval. Arrangements with providers, consultants, third-party payors, and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to healthcare providers and patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, including certain laws and regulations applicable only if we have marketed products, include the following:

- federal false claims, false statements and civil monetary penalties laws prohibiting, among other things, any person from knowingly presenting, or causing to be presented, a false claim for payment of government funds or knowingly making, or causing to be made, a false statement to get a false claim paid;
- federal healthcare program anti-kickback law, which prohibits, among other things, persons from offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual for, or the purchasing or ordering of, a good or service for which payment may be made under federal healthcare programs such as Medicare and Medicaid;
- the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), which, in addition to privacy protections applicable to healthcare providers and other entities, prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- federal laws that require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under government healthcare programs;
- federal Open Payments (or federal "sunshine" law), which requires pharmaceutical and medical device companies to monitor and report certain financial interactions with certain healthcare providers to the Center for Medicare & Medicaid Services (the "CMS"), within the HHS for re-disclosure to the public, as well as ownership and investment interests held by physicians and their immediate family members;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;

- analogous state laws and regulations, including: state anti-kickback and false claims laws; state laws requiring pharmaceutical companies to comply with specific compliance standards, restrict financial interactions between pharmaceutical companies and healthcare providers or require pharmaceutical companies to report information related to payments to health care providers or marketing expenditures; and state laws governing privacy, security and breaches of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts; and
- laws and regulations prohibiting bribery and corruption such as the FCPA, which, among other things, prohibits U.S. companies and their employees and agents from authorizing, promising, offering, or providing, directly or indirectly, corrupt or improper payments or anything else of value to foreign government officials, employees of public international organizations or foreign government-owned or affiliated entities, candidates for foreign public office, and foreign political parties or officials thereof.

Violations of these laws are punishable by criminal and/or civil sanctions, including, in some instances, exclusion from participation in federal and state health care programs, such as Medicare and Medicaid. Ensuring compliance is time consuming and costly. Similar healthcare laws and regulations exist in the EU and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers and laws governing the privacy and security of personal information.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of drug and biologic products, limiting coverage and reimbursement for medical products and other changes to the healthcare system in the U.S.

In March 2010, the U.S. Congress enacted the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the "PPACA"), which, among other things, includes changes to the coverage and payment for pharmaceutical products under government healthcare programs. Other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031.

Under current legislation, the actual reductions in Medicare payments may vary up to 4%. The Consolidated Appropriations Act, which was signed into law by President Biden in December 2022, made several changes to sequestration of the Medicare program. Section 1001 of the Consolidated Appropriations Act delays the 4% Statutory Pay-As-You-Go Act of 2010 sequester for two years, through the end of calendar year 2024. Triggered by enactment of the American Rescue Plan Act of 2021, the 4% cut to the Medicare program would have taken effect in January 2023. The Consolidated Appropriations Act's health care offset title includes Section 4163, which extends the 2% Budget Control Act of 2011 Medicare sequester for six months into fiscal year 2032 and lowers the payment reduction percentages in fiscal years 2030 and 2031.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with the enactment of the Tax Cuts and Jobs Act of 2017 (the "TCJA"), which was signed by President Trump in December 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. In June 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the PPACA after finding that the plaintiffs did not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

Pharmaceutical Prices

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the U.S. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, in December

2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, the HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program to import certain prescription drugs from Canada into the U.S. That regulation was challenged in a lawsuit by the Pharmaceutical Research and Manufacturers of America ("PhRMA") but the case was dismissed by a federal district court in February 2023 after the court found that PhRMA did not have standing to sue the HHS. Seven states (Colorado, Florida, Maine, New Hampshire, New Mexico, Texas and Vermont) have passed laws allowing for the importation of products from Canada. North Dakota and Virginia have passed legislation establishing workgroups to examine the impact of a state importation program. As of May 2024, five states (Colorado, Florida, Maine, New Hampshire and New Mexico) had submitted Section 804 Importation Program proposals to the FDA. On January 5, 2023, the FDA approved Florida's plan for Canadian product importation. That state now has authority to import certain products from Canada for a period of two years once certain conditions are met. Florida will first need to submit a pre-import request for each product selected for importation, which must be approved by the FDA. The state will also need to relabel the products and perform quality testing of the products to meet FDA standards.

Further, the HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The final rule would also eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and pharmacy benefit manager service fees. It originally was set to go into effect on January 1, 2022, but with passage of the Inflation Reduction Act of 2022 (the "IRA") has been delayed by Congress to January 1, 2032.

In August 2022, the IRA was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation; and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The law also caps Medicare out-of-pocket drug costs at $2,000 a year beginning in 2025.

The first cycle of negotiations for the Medicare Drug Price Negotiation Program commenced in the summer of 2023. On August 15, 2024, the HHS published the results of the first Medicare drug price negotiations for ten selected drugs that treat a range of conditions, including diabetes, chronic kidney disease, and rheumatoid arthritis. The prices of these ten drugs will become effective January 1, 2026. On January 17, 2025, CMS announced its selection of 15 additional drugs covered by Part D for the second cycle of negotiations by February 1, 2025. While there had been some questions about the Trump Administration's position on this program, CMS issued a public statement on January 29, 2025, declaring that lowering the cost of prescription drugs is a top priority of the new administration and CMS is committed to considering opportunities to bring greater transparency in the negotiation program. The second cycle of negotiations with participating drug companies will occur during 2025, and any negotiated prices for this second set of drugs will be effective starting January 1, 2027.

In June 2023, Merck filed a lawsuit against the HHS and CMS asserting that, among other things, the IRA's Drug Price Negotiation Program for Medicare constitutes an uncompensated taking in violation of the Fifth Amendment of the Constitution. Subsequently, a number of other parties, including the U.S. Chamber of Commerce, BMS, PhRMA, Astellas, Novo Nordisk, Janssen Pharmaceuticals, Novartis, AstraZeneca and Boehringer Ingelheim, also filed lawsuits in various courts with similar constitutional claims against the HHS and CMS. The HHS has generally won the substantive disputes in these cases, and various federal district court judges have expressed skepticism regarding the merits of the legal arguments being pursued by the pharmaceutical industry. Certain of these cases are now on appeal and, on October 30, 2024, the Court of Appeals for the Third Circuit heard oral argument in three of these cases. Litigation involving these and other provisions of the IRA will continue with unpredictable and uncertain results.

At the state level, individual states are increasingly aggressive in passing legislation and implementing 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. A number of states, for example, require drug manufacturers and other entities in the drug supply chain, including health carriers, pharmacy benefit managers, wholesale distributors, to disclose information about pricing of pharmaceuticals. In addition, regional healthcare organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription pharmaceutical and other healthcare programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Federal and State Data Privacy Laws

There are numerous U.S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. If a sponsor fails to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, it could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents.

In addition to potential enforcement by the HHS, a sponsor is also potentially subject to privacy enforcement from the Federal Trade Commission (the "FTC"). The FTC has been particularly focused on the unpermitted processing of health and genetic data through its recent enforcement actions and is expanding the types of privacy violations that it interprets to be "unfair" under Section 5 of the FTC Act, as well as the types of activities it views to trigger the Health Breach Notification Rule (which the FTC also has the authority to enforce). The agency is also in the process of developing rules related to commercial surveillance and data security. Sponsors will need to account for the FTC's evolving rules and guidance for proper privacy and data security practices in order to mitigate risk for a potential enforcement action, which may be costly.

States are also active in creating specific rules relating to the processing of personal information. In 2018, California passed into law the California Consumer Privacy Act (the "CCPA"), which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation (the "GDPR"), which is further described below, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements.

In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act (the "CPRA"), which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – the sole responsibility of which is to enforce the CPRA and other California privacy laws, which will further increase compliance risk.

In addition to California, at least eighteen other states have passed comprehensive privacy laws similar to the CCPA and CPRA. These laws are either in effect or will go into effect sometime before the end of 2026. Like the CCPA and CPRA, these laws create obligations related to the processing of personal information, as well as special obligations for the processing of "sensitive" data, which includes health data in some cases. Some of the provisions of these laws may apply to our business activities. There are also states that are strongly considering or have already passed comprehensive privacy laws during the 2024 legislative sessions that will go into effect in 2025 and beyond. Other states will be considering similar laws in the future, and Congress has also been debating passing a federal privacy law. There are also states that are specifically regulating health information that may affect our business. For example, the State of Washington passed the My Health My Data Act in 2023 which specifically regulated health information that is

not otherwise regulated by the HIPAA rules, and the law also has a private right of action, which further increases the relevant compliance risk. Connecticut and Nevada have also passed similar laws regulating consumer health data, and more states are considering such legislation in 2024. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Plaintiffs' lawyers are also increasingly using privacy-related statutes at both the state and federal level to bring lawsuits against companies for their data-related practices. In particular, there have been a significant number of cases filed against companies for their use of pixels and other web trackers. These cases often allege violations of the California Invasion of Privacy Act and other state laws regulating wiretapping, as well as the federal Video Privacy Protection Act.

Review and Approval of Drug Products in the European Union

In order to market any product outside of the U.S., a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and effectiveness and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not a company obtains FDA approval for a product candidate, it must obtain approval by the comparable regulatory authorities of foreign countries or economic areas, such as the 27-member EU, before it may commence clinical trials or market products in those countries or areas. As in the U.S., medicinal products can be marketed only if a marketing authorization from the competent regulatory agencies has been obtained. Similar to the U.S., the various phases of preclinical and clinical research in the EU are subject to significant regulatory controls.

The EU/European Economic Area ("EEA") applies harmonized regulatory rules for medicinal products, for the approval process and requirements governing the conduct of clinical trials, and for the regulatory approval of medicinal products. However, pricing and reimbursement for medicinal products varies greatly between countries and jurisdictions and can involve additional testing for health technology assessments and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Preclinical Studies

Non-clinical studies are performed to demonstrate the health or environmental safety of new chemical or biological substances. Non-clinical (pharmaco-toxicological) studies must be conducted in compliance with the principles of GLP as set forth in EU Directive 2004/10/EC (unless otherwise justified for certain particular medicinal products – e.g., radio-pharmaceutical precursors for radio-labeling purposes). In particular, non-clinical studies, both in vitro and in vivo, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organization for Economic Co-operation and Development requirements.

Clinical Trial Approval

On January 31, 2022, the new Clinical Trials Regulation (EU) No 536/2014 ("CTR") became effective in the EU and replaced the prior Clinical Trials Directive 2001/20/EC ("CTD"). The new regulation aims at simplifying and streamlining the authorization, conduct and transparency of clinical trials in the EU. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial to be conducted in more than one Member State of the EU ("EU Member State") will only be required to submit a single application for approval. The submission has to be made through the Clinical Trials Information System ("CTIS"), a new clinical trials portal overseen by the European Medicines Agency ("EMA") and available to clinical trial sponsors, competent authorities of the EU Member States and the public.

The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU Portal and Database"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the appointed reporting Member State, whose assessment report is submitted for review by the sponsor and all other competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted, or concerned member states. Part II is assessed separately by each concerned member state. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned member state. However, overall related timelines will be defined by the CTR.

The new regulation did not change the preexisting requirement that a sponsor must obtain prior approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the sponsor may only start a clinical trial at a specific clinical site after the applicable ethics committee has issued a favorable opinion.

The CTR included a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the CTD, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the CTD remain governed by said Directive until January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the CTR. As of January 31, 2025, all of our clinical trials with European sites were in compliance with this new policy.

Parties conducting certain clinical trials must, as in the U.S., post clinical trial information in the EU at the EudraCT website: https://eudract.ema.europa.eu.

Marketing Authorization

To obtain marketing authorization of a product under EU regulatory systems, a sponsor must submit a marketing authorization application ("MAA") either under a centralized or decentralized procedure/mutual recognition procedure ("MRP"). The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU member states. Pursuant to Regulation (EC) No. 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU Member States. Manufacturers must demonstrate the quality, safety, and efficacy of their products to the EMA, which provides an opinion regarding the MAA. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

Under the centralized procedure, the EMA's Committee for Medicinal Products for Human Use ("CHMP") established at the EMA is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the sponsor in response to questions of the CHMP.

The decentralized procedure or MRP is available to sponsors who wish to market a product in various EU member states where such product has not received marketing approval in any EU member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the sponsor, known as the reference member state ("RMS"). Under this procedure, a sponsor submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the RMS and concerned member states. The RMS prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the RMS's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials. If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Within this framework, manufacturers may seek approval of hybrid medicinal products under Article 10(3) of Directive 2001/83/EC. Hybrid applications rely, in part, on information and data from a reference product and new data from appropriate preclinical tests and clinical trials. Such applications are necessary when the proposed product does not meet the strict definition of a generic medicinal product, or bioavailability studies cannot be used to demonstrate bioequivalence, or there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product. In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC, as amended by Directive 2003/63/EC.

Hybrid medicinal product applications have automatic access to the centralized procedure when the reference product was authorized for marketing via that procedure. Where the reference product was authorized via the decentralized procedure, a hybrid application may be accepted for consideration under the centralized procedure if the sponsor shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a single marketing authorization for the medicinal product is in the interest of patients in the EU.

Conditional Marketing Authorization

In particular circumstances, EU legislation (Article 14–a Regulation (EC) No 726/2004 (as amended by Regulation (EU) 2019/5 and Regulation (EC) No 507/2006 on Conditional Marketing Authorizations for Medicinal Products for Human Use) enables sponsors to obtain a conditional marketing authorization prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for product candidates (including medicines designated as orphan medicinal products) if (1) the product candidate is intended for the treatment, prevention, or medical diagnosis of seriously debilitating or life-threatening diseases; (2) the product candidate is intended to meet unmet medical needs of patients; (3) the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required; (4) the risk-benefit balance of the product candidate is positive, and (5) it is likely that the sponsor will be in a position to provide the required comprehensive clinical trial data.

A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new clinical studies and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization, but sponsors can also request the EMA to conduct an accelerated assessment, for instance in cases of unmet medical needs.

Exceptional Circumstances

An MA may also be granted "under exceptional circumstances" under Article 14(8) of Regulation (EC) No 726/2004 when the applicant can show that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use even after the product has been authorized and subject to specific procedures being introduced. This may arise in particular when the intended indications are very rare and, in the present state of scientific knowledge, it is not possible to provide comprehensive information, or when generating data may be contrary to generally accepted ethical principles. This MA is close to the conditional MA as it is reserved to medicinal products to be approved for severe diseases or unmet medical needs and the applicant does not hold the complete data set legally required for the grant of a MA. However, unlike the conditional MA, the applicant does not have to provide the missing data and will never have to. Although the MA "under exceptional circumstances" is granted definitively, the risk-benefit balance of the medicinal product is reviewed annually and the MA is withdrawn in case the risk-benefit ratio is no longer favorable. Under these procedures, before granting the MA, the EMA or the competent authorities of the member states make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety, and efficacy.

PRIME Designation

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines ("PRIME") scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated MAA assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the CHMP or Committee for Advanced Therapies are appointed early in PRIME scheme, facilitating increased understanding of the product at EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Pediatric Studies

Prior to obtaining a marketing authorization in the European Union, sponsors have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan ("PIP") covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver or a deferral for one or more of the measures included in the PIP. The respective

requirements for all marketing authorization procedures are set forth in Regulation (EC) No 1901/2006, which is referred to as the Pediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Pediatric Committee of the EMA (the "PDCO") may grant deferrals for some medicines, allowing a company to delay development of the medicine in children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine in children is not needed or is not appropriate because (a) the product is likely to be ineffective or unsafe in part or all of the pediatric population; (b) the disease or condition occurs only in the adult population; or (c) the product does not represent a significant therapeutic benefit over existing treatments for the pediatric population. Before a MAA can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP.

Periods of Authorization and Renewals

Marketing authorization is valid for five years in principle and the marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file with respect to quality, safety and effectiveness, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization, or if initially placed on the market, is no longer actually present on the market for three consecutive years, ceases to be valid (the so-called sunset clause).

Regulatory Requirements after Marketing Authorization

As in the U.S., both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations. The holder of an EU marketing authorization for a medicinal product must, for example, comply with EU pharmacovigilance legislation and its related regulations and guidelines which entail many requirements for conducting pharmacovigilance or the assessment and monitoring of the safety of medicinal products. The manufacturing process for medicinal products in the EU is also highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with various requirements set out in the applicable EU laws, including compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients.

In the EU, the advertising and promotion of approved products are subject to EU Member States' laws governing the promotion of medicinal products, interactions with clinicians, misleading and comparative advertising and unfair commercial practices. Direct-to-consumer advertising of prescription medicines is prohibited across the EU. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics ("SmPC") as approved by the competent authorities. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion, which is prohibited in the EU.

Regulatory Data Protection in the EU

In the EU, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. Data exclusivity prevents sponsors for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the EU market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company can complete a full MAA with a complete independent data package of pharmaceutical test, preclinical tests and clinical trials.

In this context, it should be noted that the EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative, launched by the European Commission in November 2020. The European Commission's proposal for revision of several legislative instruments related to medicinal products was published in April 2023 and includes, among other things, provisions that would potentially reduce the duration of regulatory data protection. The European Parliament requested several amendments in April 2024. At this time, the proposed revisions remain to be agreed and adopted by the European Parliament and European Council and the proposals may therefore be substantially revised before adoption, which is not anticipated before early 2026. The revisions may, however, have a significant impact on the pharmaceutical industry in the long term, if and when adopted.

Orphan Drug Designation and Exclusivity

The criteria for designating an orphan medicinal product in the EU are similar in principle to those in the U.S. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life- threatening or chronically debilitating condition, (2) either (a) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition. The term 'significant benefit' is defined in Regulation (EC) 847/2000 to mean a clinically relevant advantage or a major contribution to patient care.

Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. During this ten-year market exclusivity period, the EMA or the competent authorities of the Member States of the EEA, cannot accept an application for a marketing authorization for a similar medicinal product for the same indication. A similar medicinal product is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The ten-year market exclusivity in the EU may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if: (1) the second sponsor can establish that its product, although similar, is safer, more effective or otherwise clinically superior; (2) the sponsor consents to a second orphan medicinal product application; or (3) the sponsor cannot supply enough orphan medicinal product.

The application for orphan designation must be submitted before the application for marketing authorization. The sponsor will receive a fee reduction for the MAA if the orphan designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Pediatric Exclusivity

If a sponsor obtains a marketing authorization in all EU Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of an SPC, or alternatively a one year extension of the regulatory market exclusivity from ten to eleven years, as selected by the marketing authorization holder.

Patent Term Extensions

The EU also provides for patent term extension through SPCs. The rules and requirements for obtaining a SPC are set out in Regulation (EC) 469/2009 and are similar to those in the U.S. An SPC may extend a patent right for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of marketing exclusivity for a drug. In certain circumstances, these periods may be extended for six additional months if pediatric exclusivity is obtained. Although SPCs are available throughout the EU, sponsors must apply on a country-by-country basis, and SPCs are valid on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the EU.

Reimbursement and Pricing Decisions for Approved Products

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that

compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, EU Member States have the option to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU Member States, and parallel trade, i.e., arbitrage between low-priced and high-priced EU Member States, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Approval of companion diagnostic devices

In the EU, medical devices such as companion diagnostics must comply with the General Safety and Performance Requirements ("SPRs") detailed in Annex I of the EU Medical Devices Regulation (Regulation (EU) 2017/745) ("MDR"), which came into force in May 2021 and replaced the previously applicable EU Medical Devices Directive (Council Directive 93/42/EEC). Compliance with SPRs and additional requirements applicable to companion medical devices is a prerequisite to be able to affix the Conformitè Europëenne mark of conformity ("CE certificate") to medical devices, without which they cannot be marketed or sold. To demonstrate compliance with the SPRs, a manufacturer must undergo a conformity assessment procedure, which varies according to the type of medical device and its classification. The MDR is meant to establish a uniform, transparent, predictable, and sustainable regulatory framework across the EU for medical devices.

Separately, the EU also adopted a new In Vitro Diagnostic Regulation (Regulation (EU) 2017/746) ("IVDR") for In vitro diagnostic medical devices ("IVDs"). The new regulation replaces the In Vitro Diagnostic Directive ("IVDD") 98/79/EC. The IVDR, among other things:

- strengthens the rules on placing devices on the market and reinforces surveillance once they are available;
- establishes explicit provisions on manufacturers' responsibilities for the follow-up of the quality, performance and safety of devices placed on the market;
- improves the traceability of medical devices throughout the supply chain to the end-user or patient through a unique identification number;
- establishes a central database to provide patients, healthcare professionals and the public with comprehensive information on products available in the EU ("EUDAMED"); and
- strengthens rules for the assessment of certain high-risk devices, such as implants, which may have to undergo an additional check by experts before they are placed on the market.

Under the IVDR, companion diagnostic devices are classified at least as a class C IVD and thus require involvement of the notified body in the regulatory approval process under the IVDR. The IVDR became effective in May 2022. However, it became clear in 2021 that that EU Member States, health institutions and economic operators were not ready to apply the IVDR as from that date. The EU thus enacted provisions on a progressive or staggered roll-out of certain rules of the IVDR in 2021 and 2024 (Regulation 2022/112 and Regulation 2023/607). Most CE certificates issued under the previous IVVD remain valid for certain transition periods, which currently range from December 31, 2027 (for IVD medical devices for which a certificate has been issued by a notified body under the IVVD and class D devices) to December 31, 2028 (for class C IVDs) and December 31, 2029 (for class B and class A sterile IVDs) These transition periods only apply to so called "legacy devices", meaning devices covered by a certificate or declaration of conformity issued under the previous legal framework (notably the IVDD). These legacy devices, benefit from the extended transition periods if they fulfil certain conditions, notably (i) that they continue to comply with the rules in force when they were placed on the market for the first time; (ii) that there are no significant changes in the design or intended purpose of the devices; (iii) that the devices do not present an unacceptable risk to the health or safety of patients, users or other persons, or to other aspects of the protection of public health and (iv) that no later than May 26, 2025, the manufacturer puts in place a quality management system compliant with the IVDR. For devices requiring an assessment by a notified body, the manufacturer must submit an application to the notified body under the IVDR to transfer the device to the IVDR by May 26, 2025 (class D devices), May 26, 2026 (class C devices) or 2027 (class B and A sterile IVDs) and execute a written contract of the notified body within four months after expiry of these application deadlines. In

addition, even for IVDs for which the transition periods apply, manufacturers have to comply with the requirements of the IVDR on post-market surveillance (PMS), market surveillance, vigilance, and registration of devices in EUDAMED.

EU General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EEA, including personal health data, is subject to the GDPR, which became effective on May 25, 2018. In the United Kingdom (the "UK"), the GDPR is retained in domestic law as the UK GDPR and sits alongside an amended version of the UK Data Protection Act 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the U.S., and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues of the respective group of companies, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Brexit and the Regulatory Framework in the United Kingdom

The UK's withdrawal from the EU, commonly referred to as Brexit, took place on January 31, 2020. The EU and the UK reached an agreement on their new partnership in the Trade and Cooperation Agreement, which entered into force on May 1, 2021. As of January 1, 2021, the Medicines and Healthcare Products Regulatory Agency (the "MHRA") became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas Northern Ireland continues to be subject to EU rules under the Northern Ireland Protocol, as amended by the so called Windsor Framework agreed in February 2023. As of January 1, 2025, the changes introduced by the Windsor Framework resulted in the MHRA being responsible for approving all medicinal products destined for the United Kingdom market (Great Britain and Northern Ireland), and the EMA will no longer have any role in approving medicinal products destined for Northern Ireland. The MHRA relies on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended) (the "HMR") as the basis for regulating medicines. The HMR has incorporated into the domestic law the body of EU law instruments governing medicinal products that pre-existed prior to the UK's withdrawal from the EU.

As of January 1, 2024 on, a new international recognition procedure ("IRP") applies which intends to facilitate approval of pharmaceutical products in the UK. The IRP is open to applicants that have already received an authorization for the same product from one of the MHRA's specified Reference Regulators ("RRs"). The RRs notably include EMA and regulators in the EEA member states for approvals in the EU centralized procedure and mutual recognition procedure as well as the FDA (for product approvals granted in the U.S.). The RR assessment must have undergone a full and standalone review. RR assessments based on reliance or recognition cannot be used to support an IRP application. A CHMP positive opinion or an MRDC positive end of procedure outcome is an RR authorisation for the purposes of IRP.

Human Capital

We believe that the success of our business is fundamentally due to our greatest asset, our employees. To that end, we have invested significant resources toward the attraction, retention and development of our people and the promotion of inclusion in our workforce. To support these goals, our human resources programs and initiatives underscore our core values (Innovation, Courage, Alignment and Accountability, Resiliency and Energy) and are designed to prioritize employees' well-being, support their career development, offer competitive wages and benefits, and enhance our culture through efforts geared toward making the workplace more enriching, engaging, and inclusive.

To attract, retain and reward our employees, we provide competitive total rewards aimed at supporting the financial, physical and emotional health of our employees and their families. We currently offer all new employees equity in our company and as incentive to all our employees in connection with our annual performance reviews. Our equity and cash incentive plans are designed to increase stockholder value and the success of our company by motivating our employees to perform to the best of their abilities and achieve our collective objectives. In addition, many of our employees are stockholders of our company through participation in our Employee Stock Purchase Plan, which aligns the interests of our employees with our stockholders by providing stock ownership on a tax-deferred basis. We also provide up to a 4% match of components of employee compensation to our Section 401(k) retirement savings plan.

We strive to provide our employees with a safe and healthy work environment and believe that the overall health, safety and wellness of our employees is critical to our long-term success and our growth as a business. As such, we provide our employees and their families with access to a variety of innovative, flexible and convenient health and wellness programs, including benefits that provide protection and security so they can have peace of mind concerning events that may require time away from work or that impact their financial well-being. In alignment with our KaryoFlex philosophy, we offer flexible time off to our employees, which is designed to provide greater flexibility and better support our employees' work-life balance. Our full-time employees are all eligible to participate in our health, vision, dental, life, and long-term disability insurance plans. To encourage employees to keep up with routine medical care and participate in our wellness program, we fund a Health Reimbursement Account for participating employees that partially covers employee deductibles and to help our employees cover medical expenses pre-tax, we also offer employees a Flexible Spending Account in addition to providing a monthly wellness fund designed to support broad well-being activities. To support our diverse populations' needs, we also offer a High Deductible Health Plan coupled with a Health Savings Account. We provide initial funding into the account and employees can also contribute to this tax-advantaged savings account that can be used to pay for medical, dental, vision, and other qualified expenses now or later in life. Along with the option to participate in a Limited Purpose Flexible Spending Account to pay for qualified dental and vision expenses throughout the year, all employees have access to complimentary virtual fitness programs, mental and emotional health support services, as well as support programs to assist working parents with childcare and tutoring. This benefit also extends to eldercare, pet care, and other needs facing our diverse global team.

We encourage and support the growth and development of our employees and, wherever possible, seek to fill positions internally, through lateral and promotional advancements and by leveraging our employee referral process. Continual learning and career development is encouraged through ongoing performance and development conversations with employees, a formal mentorship program, tuition assistance, employee and leadership training programs targeting both technical and soft skills, and customized corporate training engagements and seminars where employees are encouraged to attend in connection with current and future roles. Employees at all levels have an opportunity to develop and hone their skillsets, which provides a critically important growth path and continuity for our top performers.

Further, we strongly believe in fostering a culture of inclusiveness and employee well-being, which is key to our culture and overall success. We strive to bring together employees with a wide variety of backgrounds, skills and culture and encourage all our employees to maintain a work environment in which our differences are respected. We have put into place relationships with many local affinity groups including the biotech industry's largest LGBTQ professional group, and women and Latinos in biotech organizations to extend our reach, build relationships and foster greater cohesion among our employees.

We have created a women's Employee Resource Group ("ERG") where women and allies can connect, share experiences, and inspire one another. The ERG is a safe space for open dialogue, mentorship, and collaboration that all employees can benefit from. We have also established key working relationships with local universities where we hire many of our interns in our annual program.

As of February 14, 2025, we had 279 employees, all of whom were full-time employees. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that relations with our employees are good.

Corporate Responsibility

We are highly committed to policies and practices focused on environmental, social, and governance ("ESG"), positively impacting our social community and maintaining and cultivating good corporate governance. By focusing on ESG policies and practices, we believe we can affect a meaningful and positive change in our community and continue to cultivate our open and inclusive collaborative culture.

Some of our 2024 initiatives included continuing support for the scientific, medical, patient, and local communities in which we operate, including patient education, public health, quality of healthcare, and disease awareness. We also enable our employees to participate in various charity events, including walks, races, and other events that impact change in the communities of the patients we serve. We offer an employee volunteer time off program to support volunteer activities that enhance the communities in which we live and work while providing our employees the paid time to help those around them. This allows our employees to support causes that are meaningful to them and their families and aligns with our mission, goals, and vision.

Our ESG Report, which describes our approach to ESG programs, is available on our website at https://investors.karyopharm.com/corporate-sustainability. Information in our ESG Report is not incorporated by reference into this Form 10-K. We look forward to continuing our commitment to giving back to our local communities in 2025 and beyond.

Information about our Executive Officers

The following table lists the names, ages and positions of our executive officers as of February 14, 2025:

Name	Age	Position
Richard Paulson, M.B.A	57	President and Chief Executive Officer
Sohanya Cheng, M.B.A.	42	Executive Vice President, Chief Commercial Officer
Lori Macomber, C.P.A.	54	Executive Vice President, Chief Financial Officer and Treasurer
Michael Mano, J.D.	48	Senior Vice President, General Counsel and Secretary
Stuart Poulton	52	Executive Vice President, Chief Development Officer
Reshma Rangwala, M.D., Ph.D	47	Executive Vice President, Chief Medical Officer

Richard Paulson, M.B.A. Mr. Paulson has served as our President and Chief Executive Officer since May 2021 and as a member of our Board since February 2020. Prior to joining Karyopharm, Mr. Paulson was the Executive Vice President and Chief Executive Officer of Ipsen North America, a biopharmaceutical company, from 2018 to May 2021. Mr. Paulson was Vice President and General Manager, U.S. Oncology Business Unit at Amgen Inc. ("Amgen"), a public biotechnology company, from 2015 to 2018 and prior to that was Vice President, Marketing for Amgen's U.S. Oncology Business, General Manager, Amgen Germany and General Manager of Amgen Central & Eastern Europe. Prior to Amgen, Mr. Paulson held a number of global leadership positions at Pfizer Inc. ("Pfizer"), including serving as General Manager of Pfizer South Africa and Pfizer Czech Republic. Mr. Paulson also previously held a variety of sales, marketing, and market access roles with increasing seniority at GlaxoWellcome plc in Canada. Mr. Paulson has served as a member of the board of directors of bluebird bio, Inc., a public biotechnology company, since April 2023. Mr. Paulson has an M.B.A. from the University of Toronto, Canada and an undergraduate degree in commerce from the University of Saskatchewan, Canada.

Sohanya Cheng, M.B.A. Ms. Cheng joined Karyopharm as Senior Vice President, Sales and Commercial Operations in June 2021 and has served as our Executive Vice President, Chief Commercial Officer since December 2021. Prior to joining Karyopharm, Ms. Cheng served as Vice President, Head of Marketing, at Arrowhead Pharmaceuticals, Inc., a public pharmaceutical company, from August 2020 to December 2020. Prior to this role, Ms. Cheng spent eleven years at Amgen, a public biotechnology company, where she held a variety of sales and marketing leadership roles supporting the commercialization of key oncology brands, including as Executive Director, Head of National Sales Force & Oncology Contracting Strategy from 2019 to August 2020, Executive Director, Head of Marketing & Sales for their multiple myeloma business from 2018 to 2019; and Chief of Staff to General Manager and Strategy & Operations Director for their oncology business from 2017 to 2018. Ms. Cheng has served as a member of the board of directors of Carisma Therapeutics Inc., a public biopharmaceutical company, since October 2024. Ms. Cheng holds an M.B.A. from the MIT Sloan School of Management and a BSc and MA in Biochemistry from the University of Cambridge, United Kingdom.

Lori Macomber, C.P.A. Ms. Macomber joined Karyopharm as Executive Vice President, Chief Financial Officer and Treasurer on January 3, 2025. Prior to joining Karyopharm, Ms. Macomber served in various positions at Legend Biotech Corporation, a public biotechnology company, including as Chief Financial Officer from May 2022 to January 2025, as Vice President, Finance from March 2021 to May 2022 and as Vice President of Supply Chain Finance and Controller from 2019 to March 2021. Prior to Legend Biotech Corporation, Ms. Macomber served as Business Unit Controller at Ametek PDS, a leading supplier of components and systems for the aerospace and defense industries, from 2018 to 2019 and as U.S. Chief Financial Officer and Controller of Cello Health from 2017 until 2018. Prior to 2018, Ms. Macomber held various financial positions of increasing responsibilities within the pharmaceutical industry at Eli Lily and Company and Pfizer Inc. (formerly Pharmacia Corporation). Ms. Macomber holds a B.S. in Accounting from Pennsylvania State University and is a certified public accountant.

Michael Mano, J.D. Mr. Mano joined Karyopharm as Senior Vice President, General Counsel and Secretary in December 2020 with over 15 years of legal experience. Prior to joining Karyopharm, Mr. Mano served as Counsel, Business Development for Biogen, a public biotechnology company, from January 2018 to December 2020, where he supported Biogen's global business development platform. Prior to that he was Senior Counsel at Proskauer Rose LLP, an international law firm, from 2013 to 2018 where he represented clients in a broad range of corporate matters. Prior to Proskauer Rose LLP, Mr. Mano was in private legal practice where he represented clients in the life sciences industry in a broad range of corporate matters. Mr. Mano received a B.A. in Political Science and Sociology from Saint Michael's College and a Juris Doctor from Washington University School of Law.

Stuart Poulton. Mr. Poulton joined Karyopharm as Senior Vice President, Strategy and Portfolio Management in February 2022 and has served as our Executive Vice President, Chief Development Officer since August 2022. Mr. Poulton served as Vice President, Clinical Development Operations at AbbVie Inc., a public biopharmaceutical company, from 2019 to January 2022 and as Vice President, Portfolio Program Management from 2016 to 2019. Prior to that, Mr. Poulton served in several roles at Amgen, including as

Executive Director, Global Program Management from 2013 to 2016; as Director, Global Program Management, Asia Regional Management Team, from 2012 to 2013; as Director, Global Program Management, from 2007 to 2012 and as Senior Manager, Clinical Study Planning from 2006 to 2007. Mr. Poulton started his career at Eli Lilly and Company in clinical operations. Mr. Poulton received his B.Sc. in Pharmacology and Chemistry from the University of Sydney, Australia and a M.Com. in Marketing from the University of New South Wales, Australia.

Reshma Rangwala, M.D., Ph.D. Dr. Rangwala joined Karyopharm in April 2022 as Executive Vice President, Chief Medical Officer, with more than a decade of experience in oncology and drug development. Dr. Rangwala served as Chief Medical Officer of Aravive, Inc., a public oncology company, from September 2020 to April 2022. Prior to that, Dr. Rangwala served as Vice President, Medical, at Genmab Inc., an international biotechnology company, from 2017 to July 2020. Prior to that, Dr. Rangwala served as Executive Clinical Director at Merck & Co., a biopharmaceutical company, from 2012 to 2017. Dr. Rangwala received her B.S. in Biology from Duke University and her M.D./Ph.D. from the University of Cincinnati College of Medicine. She completed her internal medicine residency at Barnes Jewish Hospital in St. Louis, Missouri and her medical oncology fellowship at the Hospital of the University of Pennsylvania.

Information about our Directors

The following table lists the names, ages and positions of our current directors:

Name	Age	Position
Richard Paulson, M.B.A.	57	President and Chief Executive Officer of Karyopharm
Barry E. Greene	61	Chief Executive Officer of Sage Therapeutics, Inc., a biopharmaceutical company
Garen G. Bohlin	77	Former Executive Vice President of Constellation Pharmaceuticals, Inc., a biopharmaceutical company
Mansoor Raza Mirza, M.D.	63	Chief Oncologist at the Department of Oncology, Rigshopitalet – the Copenhagen University Hospital, Denmark and Medical Director of the Nordic Society of Gynaecological Oncology
Christy J. Oliger	55	Former Senior Vice President of the Oncology Business Unit at Genentech, Inc., a biotechnology company
Deepa R. Pakianathan, Ph.D.	60	Managing Member at Delphi Ventures, a venture capital firm focused on biotechnology and medical device investments
Chen Schor	52	President, Chief Executive Officer and Director of Adicet Bio, Inc., a biotechnology company
Zhen Su, M.D., M.B.A.	48	Chief Executive Officer and Director of Marengo Therapeutics, Inc., a biotechnology company

Available Information

Our Internet website is https://www.karyopharm.com. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the U.S. Securities and Exchange Commission. In addition, we regularly use our website to post information regarding our business, development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "*Investors*" as a source of information about us. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Annual Report on Form 10-K.

Our Code of Business Conduct and Ethics, Corporate Governance Guidelines and the charters of the Audit, Compensation, Nominating, Corporate Governance & Compliance and Commercialization and Portfolio Committees of our Board of Directors are all available on our website at https://www.karyopharm.com at the "Investors" section under "Corporate Governance." Stockholders may request a free copy of any of these documents by writing to Investor Relations, Karyopharm Therapeutics Inc., 85 Wells Avenue, 2nd floor, Newton, Massachusetts 02459, U.S.A.

Item 1A. Risk Factors.

Careful consideration should be given to the following material risk factors, in addition to the other information set forth in this Annual Report on Form 10-K and in other documents that we file with the U.S. Securities and Exchange Commission ("SEC") in evaluating us and our business. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occurs, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks we face. New risk factors can emerge from time to time, and it is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition and results of operations.

References to XPOVIO® (selinexor) also refer to NEXPOVIO® (selinexor) when discussing its approval and commercialization in certain countries or territories outside of the U.S.

Risks Related to Commercialization and Product Development

Our business is substantially dependent on the commercial success of XPOVIO. If we, either alone or with our collaborators, are unable to successfully commercialize current and future indications of XPOVIO or other products or product candidates on a timely basis, including achieving widespread market acceptance by physicians, patients, third-party payors and others in the medical community, our business, financial condition and future profitability will be materially harmed.

Our business and our ability to generate product revenue from the sales of drugs that treat cancer depend heavily on our and our collaborators' ability to successfully commercialize our lead drug, XPOVIO® (selinexor), on a global basis in currently approved and future indications, and the level of market adoption for, and the continued use of, our products and product candidates, if approved. XPOVIO is currently approved and marketed in the U.S. in multiple hematologic malignancy indications, including in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody; and under accelerated approval as a monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma ("DLBCL"), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. Efforts to drive adoption within the medical community and third-party payors based on the benefits of our products and product candidates require significant resources and may not be successful. The success of XPOVIO and any current or future product candidates, whether alone or in collaboration with third parties, including achieving and maintaining an adequate level of market adoption, depends on several factors, including:

- our ability to achieve broad adoption of XPOVIO in earlier lines of therapy or to successfully launch and achieve broad adoption of any future XPOVIO indications or any product candidates for which we obtain marketing approval;
- the competitive landscape for our products, including the timing of new competing products entering the market and the level and speed at which these products achieve market acceptance;
- actual or perceived advantages or disadvantages of our products or product candidates as compared to alternative treatments, including their respective safety, tolerability and efficacy profiles, the potential convenience and ease of administration, access or cost effectiveness;
- the effectiveness of our sales, marketing, manufacturing and distribution strategies and operations;
- the consistency of any new data we collect and analyses we conduct with prior results, whether they support a favorable benefit-risk profile of XPOVIO and any potential impact on our U.S. Food and Drug Administration ("FDA") approvals and/or FDA package insert for XPOVIO and comparable foreign regulatory approvals and package inserts;
- our ability to comply with the FDA's and comparable foreign regulatory authorities' post-marketing requirements and commitments, including through successfully conducting, on a timely basis, additional studies that confirm clinical efficacy, effectiveness and safety of XPOVIO and acceptance of the same by the FDA or similar foreign regulatory bodies;
- acceptance of current indications of XPOVIO and future indications of XPOVIO and other product candidates, if approved, by patients, the medical community and third-party payors;
- obtaining and maintaining coverage, adequate pricing and reimbursement by third-party payors, including government payors, for XPOVIO and our product candidates, if approved;

- the willingness of patients to pay out-of-pocket in the absence of third-party coverage or as co-pay amounts under third-party coverage; for example, multiple myeloma foundation closures during 2023 resulted in significantly increased use of our Patient Assistance Program ("PAP"), which adversely impacted our 2023 revenues;
- our ability to enforce intellectual property rights in and to our products to prohibit a third-party from marketing a competing product and our ability to avoid third-party patent interference or intellectual property infringement claims;
- current and future restrictions or limitations on our approved or future indications and patient populations or other adverse regulatory actions;
- the performance of our manufacturers, license partners, distributors, providers and other business partners, over which we have limited control;
- any significant misestimations of the size of the market and market potential for any of our products or product candidates;
- establishing and maintaining commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- the willingness of the target patient population to try new therapies or new treatment paradigms such as bridging therapies and of physicians to prescribe these therapies, based, in part, on their perception of our clinical trial data and/or the actual or perceived safety, tolerability and effectiveness profile;
- maintaining an acceptable safety and tolerability profile of our approved products, including the prevalence and severity of any side effects;
- the ability to offer our products for sale at competitive prices;
- adverse publicity about our products or favorable publicity about competitive products; and
- our ability to maintain compliance with existing and new health care laws and regulations, including government pricing, price reporting and other disclosure requirements related to such laws and regulations, and the potential impact of such laws and regulations on physician prescribing practices and payor coverage.

If we do not achieve one or more of these factors in a timely manner, or at all, either on our own or with our collaborators, we could experience significant delays or an inability to successfully commercialize XPOVIO or our product candidates, if approved, which would materially harm our business.

We face substantial competition, which may result in others discovering, developing or commercializing drugs before or more successfully than we do.

The discovery, development and commercialization of new drugs is highly competitive, particularly in the cancer field. We and our collaborators face competition with respect to XPOVIO and will face competition with respect to any product candidates that we may seek to discover and develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, academic institutions and governmental agencies as well as public and private research institutions worldwide, many of which have significantly greater financial resources and expertise in research and development, manufacturing, preclinical studies, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. There are a number of major pharmaceutical, specialty pharmaceutical and biotechnology companies that currently market and sell drugs and/or are pursuing the development of drugs for the treatment of cancer and the other disease indications for which we, and our collaborators, are developing our product candidates. Several new novel therapeutics have recently entered, and are expected to continue to enter, the multiple myeloma treatment landscape. For example, TECVAYLI™ (teclistamab-cqyv), the first bispecific T-Cell engager, was approved by the FDA in October 2022, followed by approvals of two more bispecifics, ELREXFIO™ (elranatamab-bcmm) and TALVEY™ (talquetamab-tgvs) in August 2023. Other T-cell engaging therapies, bispecifics with different targets, and immunomodulators are in clinical development and may be introduced into the multiple myeloma market in 2025 and beyond. CARVYKTI® (ciltacabtagene autoleucel; cilta-cel) and Abecma® (idecabtagene vicleucel; ide-cel) were approved in April 2024 for the treatment of multiple myeloma in earlier lines. In addition, new competitors and label expansions into earlier lines of existing therapies could also be approved in the future (e.g. belantamab mafodotin and linvoseltamab), which could negatively impact our product revenues. The approval of these anti-cancer agents, or any others which may receive regulatory approval, have had a significant impact and may continue to have a significant impact on the therapeutic landscape and our product revenues. See Item 1 under the heading *Business - Competition* in this Annual Report on Form 10-K for more information on competition.

We are currently focused on developing and commercializing our products and product candidates for the treatment of cancer and there are a variety of available therapies marketed for cancer. In many cases, cancer drugs are administered in combination to

enhance efficacy. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well-established therapies and are widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic drugs. Our products are priced at a significant premium over competitive generic drugs, which may make it difficult for us to achieve our business strategy of using our products in combination with existing therapies or replacing existing therapies with our products.

Further, our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are or are perceived to be more effective, safer, more tolerable, more convenient and/or less costly than any of our currently approved products or product candidates or that would render our products obsolete or non-competitive. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for their products more rapidly than we, or our collaborators, may obtain approval for ours, which could result in our competitors establishing a stronger market position before we, or our collaborators, are able to enter the market or preventing us, or our collaborators, from entering into a particular indication at all.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or that may be necessary for, our programs.

If we are not able to compete effectively against current or potential competitors, our business will not grow and our financial condition and operations will suffer.

Clinical development is a lengthy and expensive process, with uncertain timelines and outcomes. We or our collaborators may be unable to successfully enroll patients in our ongoing and planned clinical trials in a reasonable timeframe, or at all. In addition, if clinical trials of our product candidates fail to demonstrate safety and effectiveness to the satisfaction of regulatory authorities or do not otherwise produce positive results, we, or our collaborators, may incur additional costs, fail to secure regulatory approvals, or be unable to commercialize such product candidates.

Our long-term success depends in a large part on our ability to continue to successfully develop new indications of selinexor, our product candidates, or any new product candidates we may develop or acquire. Clinical testing is expensive, time consuming, difficult to design, implement and enroll, inherently uncertain as to outcome, and can fail at any stage of testing. Furthermore, the failure of any product candidates to demonstrate safety and effectiveness in any clinical trial could negatively impact the perception of selinexor or our other product candidates and/or cause the FDA or other regulatory authorities to require additional testing before any of our product candidates are approved.

Numerous unforeseen events during, or as a result of, clinical trials could delay or prevent our or our collaborators' ability to complete such clinical trials or receive marketing approval of our product candidates, including, but not limited to, the following:

- delays or failure to reach agreement with regulatory authorities on a trial design or the receipt of feedback requiring us to modify the design of our clinical trials, perform additional or unanticipated clinical trials to obtain approval or alter our regulatory strategy, as is the case in connection with the feedback we received from the FDA in February 2022 on our SIENDO trial and the feedback from the FDA that we announced in December 2024 regarding the appropriateness of our global, Phase 3 trial evaluating selinexor as a maintenance therapy following systemic therapy in patients with *TP53* wild-type advanced or recurrent endometrial cancer (the "EC-042 Trial") given the evolving treatment landscape for patients with advanced or recurrent endometrial cancer;
- clinical trials of our product candidates may produce negative or inconclusive results or other patient safety concerns, including undesirable side effects or other unexpected characteristics, and we may decide, or regulatory authorities may require us, to conduct additional clinical trials, suspend ongoing clinical trials or abandon drug development programs, including as a result of a finding that the participants are being exposed to unacceptable health risks;
- enrollment in our clinical trials may be slower than we anticipate, including as a result of competition with other ongoing clinical trials or recently approved agents, which could decrease the overall supply of patients, or decreasing interest from selected clinical trial sites, delays in site activation, higher than expected screen failure rates, newly approved competitive products for the same indications as our product candidates or new or amended regulations; for example, in August 2024, we announced expected delays in our top-line data readout for our EC-042 Trial due primarily to higher than expected screen failure rates, which has required us to screen a larger number of patients than originally planned;
- changes in the treatment landscape on which a clinical development plan was based, such as the approval of new therapies during the course of a clinical trial, can change the potential approvability of a drug even if the results of a pivotal, Phase

3 clinical trial are considered clinically meaningful and the primary endpoints achieve statistical significance since global regulatory agencies, including the FDA, often consider approvability in light of the current treatment landscape at the time of approval, and not at the time when a clinical trial is first designed; for example, in recent years three new novel agents (dostarlimab-gxly, pembrolizumab and durvalumab) have been approved for treatment in patients with endometrial cancer, which has evolved the treatment landscape;

- modifications of clinical trial protocols impacting the patient population under study, including any modifications to the eligibility criteria or the total number of patients targeted for enrollment;
- strategic revisions to clinical trial designs, including a change in primary endpoints or a reduction in the total number of patients targeted for enrollment, which could negatively impact our ability to submit and/or receive regulatory approval for the indication sought; for example, we recently decreased the number of total patients to be enrolled in the ongoing Phase 3 trial evaluating selinexor in combination with pomalidomide and dexamethasone versus elotuzumab, pomalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma;
- regulators may revise the requirements for approving our product candidates, even after providing a positive opinion on or otherwise reviewing and providing comments to a clinical trial protocol, and/or such requirements may not be as we anticipate;
- delays or failure in obtaining the necessary authorization from regulatory authorities or ethics committees, including institutional review boards, to permit us, our collaborators or our investigators to commence a clinical trial, conduct a clinical trial at a prospective trial site, or the suspension or termination of a clinical trial once commenced;
- delays or failure to reach agreement on acceptable terms with prospective clinical trial sites or contract research organizations ("CROs");
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate, which can increase the cost of our trials, extend clinical trial timelines and provide competitors with additional time to seek regulatory approval for their products prior to the finalization of our trials;
- our third-party contractors, including manufacturers or CROs, may fail to comply with regulatory requirements, perform effectively, or meet their contractual obligations to us in a timely manner, or at all;
- we or our investigators might be found to be non-compliant with regulatory requirements;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials may be insufficient or inadequate;
- for any biomarker driven clinical trial, the potential regulatory requirement to develop one or more companion diagnostics; for example, the required development of companion diagnostics for our ongoing clinical trial evaluating selinexor in patients with *TP53* wild-type advanced or recurrent endometrial cancer;
- any partners or collaborators that help us conduct clinical trials may face any of the above issues, and may conduct clinical trials in ways they view as advantageous to them but that are suboptimal for us; and
- negative impacts resulting from a pandemic or other public health emergency, including impacts to healthcare systems and our trial sites' ability to conduct trial.

If we, or our collaborators, are required to conduct additional clinical trials or other testing of our product candidates or a companion diagnostic beyond those that we currently contemplate or are unable to successfully complete clinical trials of our product candidates or other testing, on a timely basis or at all, if changes to the external landscape impact our planned patient population or current clinical trial protocols, and/or if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we, or our collaborators, may:

- need to delay, limit or terminate ongoing or planned clinical trials;
- be delayed in obtaining, or not obtain at all, marketing approval for the indication or product candidate;
- obtain marketing approval in some countries and not in others;
- obtain approval for indications or patient populations that are not as broad as intended or desired;

- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements;
- not receive royalty or milestone revenue under our collaboration agreements for several years, or at all; or
- have the product removed from the market after obtaining marketing approval.

Further, we do not know whether clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. In addition, if we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted. For example, in December 2022, with the passage of Food and Drug Omnibus Reform Act ("FDORA"), Congress required sponsors to develop and submit a Diversity Action Plan ("DAP") for each Phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. In June 2024, as mandated by FDORA, the FDA issued draft guidance outlining the general requirements for DAPs. Unlike most guidance documents issued by the FDA, the DAP guidance when finalized will have the force of law because FDORA specifically dictates that the form and manner for submission of DAPs are specified in FDA guidance. On January 27, 2025, in response to an Executive Order issued by President Trump on January 21, 2025, on Diversity, Equity and Inclusion programs, the FDA removed this draft guidance from its website. This action raises questions about the applicability of statutory obligations to submit DAPs and the agency's current thinking on best practices for clinical development.

Similarly, the regulatory landscape related to clinical trials in the EU recently evolved. The CTR, which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. While the Clinical Trials Directive required a separate clinical trial application to be submitted in each member state, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned.

Any of these events could prevent us or our collaborators from achieving or maintaining market acceptance of the affected product candidate, if approved, or could substantially increase costs and expenses of development or commercialization, which could delay or prevent us from generating sufficient revenue from the sale of our products and harm our business and results of operations. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our products, allow our competitors to bring products to market before we do or impair our ability to successfully commercialize our products, which would harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of regulatory approval of our product candidates.

Serious adverse or unacceptable side effects related to XPOVIO, our product candidates or future products may delay or prevent their regulatory approval, cause us or our collaborators to suspend or discontinue clinical trials, limit the commercial value of approved indications or result in significant negative financial consequences following any marketing approval.

We are currently developing selinexor for the treatment of multiple types of cancer. Its risk of failure is high. If our current or future indications of XPOVIO, any of our product candidates or future products are associated with undesirable side effects or have characteristics that are unexpected in clinical trials or following approval and/or commercialization, we may need to abandon or limit their development or limit marketing to certain 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.

Adverse events ("AEs") in our clinical trials for selinexor to date have been generally predictable and typically manageable, including through prophylactic care or dose reductions, although some patients have experienced more serious AEs. The most common drug-related AEs in our clinical trials for selinexor include fatigue, nausea, anorexia, diarrhea, peripheral neuropathy, upper respiratory tract infection, vomiting, cytopenias, hyponatremia, weight loss, decreased appetite, cataract, dizziness, syncope, depressed level of consciousness, and mental status changes. These side effects were generally mild or moderate in severity. The most common AEs that are Grade 3 or Grade 4, meaning they are more than mild or moderate in severity, include thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia. To date, the most common AEs in the multiple myeloma patient population have been managed with supportive care and dose modifications. However, a number of patients have withdrawn from our clinical trials as a result of AEs and some patients across our clinical trials have experienced serious AEs deemed by us and the clinical investigator to be related to selinexor. Serious AEs generally refer to AEs that result in death, are life threatening, require hospitalization or prolonging of hospitalization, or cause a significant and permanent disruption of normal life functions, congenital anomalies or birth defects, or require intervention to prevent such an outcome.

The occurrence of AEs in either our clinical trials or following regulatory approval could result in a more restrictive label for any product candidates approved for marketing or could result in the delay or denial of approval to market any product candidates by the FDA or comparable foreign regulatory authorities, which could prevent us from generating sufficient revenue from product sales or ultimately achieving profitability. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial, result in potential product liability claims or cause patients and/or healthcare providers to elect alternative courses of treatment. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. Inadequate training or education of healthcare professionals to recognize or manage the potential side effects of XPOVIO or our product candidates, if approved, could result in increased treatment-related side effects and cause patients to discontinue treatment. Any of these occurrences may harm our business, financial condition and prospects significantly.

Results of our trials could reveal an unacceptably high severity and prevalence of side effects. In such an event, our trials could be suspended or terminated by us or the FDA or comparable foreign regulatory authorities could order us or our collaborators to cease further development of or deny approval of our product candidates for any or all targeted indications. Many compounds that initially showed promise in early-stage trials for treating cancer or other diseases have later been found to cause side effects that prevented further development of the compound. If such an event occurs after any of our or our collaborators' product candidates are approved and/or commercialized, a number of potentially significant negative consequences may result, including:

- regulatory authorities may withdraw the approval of such drug, require additional warnings on the label or impose distribution or use restrictions and/or require one or more post-marketing studies;
- patients and/or healthcare providers may elect to utilize other treatment options that have or are perceived to have more tolerable side effects;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Further, we, our collaborators and our clinical trial investigators, currently determine if serious adverse or unacceptable side effects are drug-related. The FDA or foreign regulatory authorities may disagree with our, our collaborators' or our clinical trial investigators' interpretation of data from clinical trials and the conclusion by us, our collaborators or our clinical trial investigators that a serious adverse effect or unacceptable side effect was not drug-related. The FDA or foreign regulatory authorities may require more information related to the safety of our products or product candidates, including additional preclinical or clinical data to support approval, which may cause us to incur additional expenses, delay or prevent the approval of one of our product candidates, and/or delay or cause us to change our commercialization plans, or we may decide to abandon the development of the product candidate altogether.

The results of previous clinical trials may not be predictive of future trial results, and interim or top-line data may be subject to change or qualification based on the complete analyses of data and, therefore, may not be predictive of the final results of a trial.

Clinical failure can occur at any stage of the clinical development process and, therefore, the outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later stage clinical trials. Finalization and cleaning of data from our clinical trials may change the conclusions drawn from uncleaned data provided by our clinical trial investigators. Further, 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 size and type of the patient populations, starting dose, adherence to the dosing regimen and other trial protocols and the dropout rate among clinical trial participants. We do not know whether any Phase 2, Phase 3 or other clinical trials we may conduct will demonstrate consistent or adequate efficacy and safety data sufficient to obtain regulatory approval to market our product candidates, if approved. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks.

We may publicly disclose preliminary, interim or top-line data from our clinical trials. These interim updates are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change as further patient data become available and following a more comprehensive review of the data related to the particular study or trial. For any trial for which we report preliminary, interim or top-line data, we make assumptions, estimations, calculations and conclusions as part of our analyses of data. We may not have received or had the opportunity to fully and carefully evaluate all data or perform all analyses or our conclusions may differ from those of the FDA or other regulatory authorities. Consequently, the interpretation of preliminary, interim or top-line data results that we report may differ from future interpretations of the same studies once additional data have been received and fully evaluated or based on differing views from regulatory agencies. Preliminary, interim or 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, these early data points should be viewed with caution until the final data are available. Adverse differences between previous preliminary or interim data and future interim or final data could significantly harm our business.

In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically selected from a more extensive amount of available information. Furthermore, we may report interim analyses of only certain endpoints rather than all endpoints. Investors may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business.

If the interim or top-line data that we report differ from future or more comprehensive data, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for and commercialize our product candidates, our business, operating results, prospects, or financial condition may be harmed.

We may not be successful in our efforts to identify or discover additional potential product candidates, or our decisions to prioritize the development of certain product candidates over others may later prove wrong.

Part of our strategy involves identifying and developing product candidates to build a pipeline of product candidates. Our drug discovery efforts may not be successful in identifying compounds that are useful in treating cancer or other diseases. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential product candidates;
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval and/or achieve market acceptance; or
- potential product candidates may not be effective in treating their targeted diseases.

We are currently advancing multiple clinical development studies of selinexor, which may create a strain on our limited human and financial resources. As a result, we may not be able to provide sufficient resources to any single product candidate to permit the successful development and commercialization of such product candidate, which could result in material harm to our business. Further, because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. For example, as announced in January 2024, further clinical development of our eltanexor program continues to remain on hold in an effort to focus our resources on our prioritized late-stage programs. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any additional 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 to such product candidate.

If we are unable to maintain or expand our sales, marketing and distribution capabilities, we may not be successful in commercializing XPOVIO or any of our products or product candidates, if approved, that we may acquire or develop.

We have built a commercial infrastructure in the U.S. for XPOVIO, our first commercial product, in hematological malignancies and our company did not previously have any prior experience in the sales, marketing or distribution of pharmaceutical drugs. If XPOVIO or any of our product candidates is approved for additional indications beyond hematological malignancies, such as solid tumors, we may need to evolve our sales, marketing and distribution capabilities and we may not be able to do so successfully or on a timely basis. In the future, we may choose to expand our sales, marketing and distribution infrastructure to market or co-promote one or more of our product candidates, if and when they are approved, or enter into additional collaborations with respect to the sale, marketing and distribution of our product candidates. We are working with existing and potential partners to establish the commercial infrastructure to support the sale of selinexor outside of the U.S. For example, we entered into a license agreement with the Menarini Group ("Menarini") in December 2021, and as amended in March 2023, to, among other things, develop and commercialize NEXPOVIO for all human oncology indications in Europe (including the United Kingdom ("UK")), Latin America, certain Middle East and Africa regions and other key countries. For additional risks associated with commercializing our products outside of the U.S., please see the risk factor entitled "*We depend on collaborations with third parties for certain aspects of the development, marketing and/or commercialization of XPOVIO and/or our product candidates. If those collaborations are not successful, or if we are not able to maintain our existing collaborations or establish additional collaborations, we may have to alter our development and commercialization plans and may not be able to capitalize on the market potential of XPOVIO or our product candidates*" below.

There are risks involved with establishing and maintaining our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time consuming and could delay any commercial launch of a product candidate or negatively impact ongoing commercialization efforts for our approved products. Further, we may underestimate the size of the sales force required for a successful product launch and we may need to expand our sales force earlier and at a higher cost than we anticipated. If the commercial launch of any of our product candidates is delayed or does not occur for any reason, including if we do not receive marketing approval in the timeframe we expect, we may have prematurely or unnecessarily incurred commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to successfully commercialize XPOVIO or any product candidates, if approved, on our own include:

- existing or new competitors taking share from XPOVIO or any other future product or preventing XPOVIO or any other future product from gaining share in its approved indications;
- our inability to recruit, train and retain adequate numbers of effective sales, market access, market analytics, operations and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe current or future products;
- the lack of complementary drugs, which may put us at a competitive disadvantage relative to companies with more extensive drug lines;
- unforeseen costs and expenses associated with creating an independent sales, marketing and distribution organization;
- our inability to obtain sufficient coverage and reimbursement from third-party payors and governmental agencies; and
- our ability to supply sufficient inventory of our products for commercial sale.

Even if we, or our collaborators, are able to effectively commercialize XPOVIO or any approved products that we may develop or acquire, the products may not receive coverage or may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, all of which would harm our business.

The legislation and regulations that govern marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. As a result, we or our collaborators might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay the commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we, or our collaborators, are able to generate from product sales in that country. In the U.S., approval and reimbursement decisions are not linked directly, but there is increasing scrutiny from the Congress, regulatory authorities, payers, patients and pathway organizations of the pricing of pharmaceutical products. Adverse pricing limitations may also hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our, and our collaborators', ability to successfully commercialize XPOVIO and any other products that we may develop or acquire will depend, in part, on the extent to which reimbursement for these products is available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. Obtaining and maintaining adequate reimbursement for XPOVIO and any of our product candidates, if approved, may be difficult. Moreover, the process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payor will pay for the product. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for our products. Even with payer coverage, patients may be unwilling or unable to pay the copay required and may choose not to take XPOVIO.

A primary trend in the healthcare industry in the U.S. 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 medications. 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. Third-party payors may also seek, with respect to an approved product, additional clinical evidence that goes beyond the data required to obtain marketing approval. They may require such evidence to demonstrate clinical benefits and value in specific patient populations or they may call for costly pharmaceutical studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies before covering our products. Accordingly, we cannot be sure that reimbursement will be or will continue to be available for XPOVIO and any product that we, or our collaborators, commercialize and, if reimbursement is available, we cannot be sure as to the level of reimbursement and whether it will be adequate. Coverage and

reimbursement may impact the demand for or the price of XPOVIO or any product candidate for which we, or our collaborators, obtain marketing approval. If reimbursement is not available or is available only at limited levels, we, or our collaborators, may not be able to successfully commercialize XPOVIO or any other approved products.

There may be significant delays in obtaining reimbursement for newly-approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. 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. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize our products and our overall financial condition.

Product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of XPOVIO or any other products that we may develop or acquire.

We face an inherent risk of product liability exposure related to our commercialization of XPOVIO and the testing of our product candidates in human clinical trials as the administration of our products to humans may expose us to liability claims, whether or not our products are actually at fault for causing any harm or injury. As XPOVIO is used over longer periods of time by a wider group of patients taking numerous other medicines or by patients with additional underlying conditions, the likelihood of adverse drug reactions or unintended side effects, including death, may increase. For example, we may be sued if any drug we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against claims that our products or product candidates caused injuries, we will incur substantial liabilities or be required to limit commercialization of our products. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for XPOVIO and any other products that we may develop or acquire;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to successfully commercialize XPOVIO and any other products that we may develop or acquire.

We currently hold clinical trial and general product liability insurance coverage, but that coverage may not be adequate to cover any and all liabilities that we may incur. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

The business that we or our collaborators conduct outside of the U.S. may be adversely affected by international risks and uncertainties.

Although our operations are primarily based in the U.S., we and our collaborators conduct business outside of the U.S. and expect to continue to do so in the future. For instance, many of the sites at which our clinical trials are being conducted are located outside of the U.S. In addition, we and our collaborators are seeking and continue to plan to seek approvals to sell our and their products in foreign countries. Any business that we, or our collaborators, conduct outside of the U.S. is subject to additional risks that may materially adversely affect our or their ability to conduct business in international markets, including:

- potentially reduced protection of our intellectual property rights;
- the potential for so-called parallel importing, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from a foreign market (with low or lower prices) rather than buying them locally;
- unexpected changes in tariffs, trade barriers or regulatory requirements;
- economic weakness, including the uncertainty associated with worldwide economic conditions as a result of inflation, sustained high interest rates, natural disasters and military conflicts, including the conflict between Russia and Ukraine, the war between Israel and Hamas, the Palestinian group that controls the Gaza Strip, volatility in currency exchange rates, pandemics or other public health emergencies, or political instability in particular foreign economies and markets;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- production shortages resulting from any events affecting a product candidate and/or finished drug product supply or manufacturing capabilities abroad;
- business interruptions resulting from geo-political actions, including war and terrorism, such as the ongoing conflict between Russia and Ukraine, the war between Israel and Hamas, pandemics or other public health emergencies, climate change or natural disasters, including earthquakes, hurricanes, typhoons, floods and fires; and
- failure to comply with Office of Foreign Asset Control rules and regulations and the Foreign Corrupt Practices Act ("FCPA").

Risks Related to Regulatory Matters

Even if we, or our collaborators, complete the necessary preclinical studies and clinical trials for our product candidates, the regulatory approval process is expensive, time consuming and uncertain and we or they may not receive approvals for the commercialization of some or all of our or their product candidates in a timely manner, or at all.

Our long-term success and ability to sustain and grow revenue depends on our and our collaborators' ability to continue to successfully develop our product candidates and obtain regulatory approval to market our or their products both in and outside of the U.S. In order to market and sell our products in the EU and many other jurisdictions, we and our collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The FDA and comparable foreign regulatory authorities, whose laws and regulations may differ from country to country, impose substantial requirements on the development of product candidates to become eligible for marketing approval and have substantial discretion in the process and may refuse to accept any application or may decide that the data are insufficient for approval and require additional preclinical studies, clinical trials or other studies and testing. The time required to obtain approval outside of the U.S. may differ substantially from that required to obtain FDA approval. For example, in many countries outside of the U.S., it is required that the drug be approved for reimbursement before the drug can be approved for sale in that country. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside of the U.S. does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in other countries. For additional risks related to conducting business outside of the U.S., please see the risk factor above entitled "*The business that we or our collaborators conduct outside of the U.S. may be adversely affected by international risks and uncertainties*."

In addition, the FDA and foreign regulatory authorities retain broad discretion in evaluating the results of our clinical trials and in determining whether the results demonstrate that selinexor or any other product candidate is safe and effective. If we are required to conduct additional clinical trials of selinexor or other product candidates prior to approval of additional indications, in earlier lines of therapy or in combination with other drugs, including additional earlier phase clinical trials that may be required prior to commencing any later phase clinical trials, or additional clinical trials following completion of our current and planned later phase clinical trials, we may need substantial additional funds, and there is no assurance that the results of any such additional clinical trials will be sufficient for approval.

The process of obtaining marketing approvals, both in the U.S. and abroad, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information, including manufacturing information, to regulatory authorities for each therapeutic indication to establish the product candidate's safety and effectiveness. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application.

The FDA or other regulatory authorities may determine that (i) our product candidates do not have an overall positive benefit-risk profile; (ii) the dose used in a clinical trial has not been optimized and require us to conduct additional dose optimization studies; or (iii) the comparator arm and/or endpoint in a trial is no longer the appropriate comparator or endpoint due to the evolution of the competitive landscape or subsequent data of the comparator product, even if the FDA or other regulatory authority had previously approved the trial design, and we may be required to amend the trial or we may not receive approval of the indication. For example, in December 2024, we announced that we were engaged in discussions with the FDA regarding the evolving treatment landscape in advanced or recurrent endometrial cancer, particularly the approval of checkpoint inhibitors (e.g., pembrolizumab, dostarlimab-gxly and durvalumab). We intend to submit to the FDA and other relevant global regulatory authorities an amendment to the EC-042 Trial protocol incorporating modifications, which we believe are responsive to certain of the FDA's concerns. However, the FDA may not agree that some or all of our proposed modifications to the EC-042 Trial adequately address their concerns, which may ultimately impact approvability. In addition, the FDA's Oncology Center of Excellence has a number of projects to advance the development and regulation of medical products for patients with cancer, such as Project Optimus to reform the dose optimization and dose selection paradigm in oncology drug development to emphasize selection of an optimal dose. These projects exemplify the emphasis the FDA is placing on various elements in the drug development process and therefore may require sponsors to spend additional time and resources either pre- or post-approval, and our ability to complete existing trials or initiate new trials may be delayed.

Moreover, clinical investigators for our clinical trials may serve as scientific advisors or consultants to us and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or a comparable foreign regulatory authority may conclude that a financial relationship between us and a clinical investigator has created a conflict of interest or otherwise affected interpretation of the trial. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

Further, under the Pediatric Research Equity Act ("PREA"), an NDA or supplement to an NDA for certain drugs must contain data to assess the safety and effectiveness of the drug in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective, unless the sponsor receives a deferral or waiver from the FDA. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The law requires the FDA to send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation. It further requires the FDA to publicly post the PREA Non-Compliance letter and sponsor's response. The applicable legislation in the EU also requires sponsors to either conduct clinical trials in a pediatric population in accordance with a Pediatric Investigation Plan approved by the Pediatric Committee of the European Medicines Agency ("EMA") or to obtain a waiver or deferral from the conduct of these studies by this Committee. For any of our product candidates for which we or our collaborators are seeking regulatory approval in the U.S. or the EU, we cannot guarantee that we will be able to obtain a waiver or alternatively complete any required studies and other requirements in a timely manner, or at all, which could result in an issuance and publication of a PREA Non-Compliance letter and associated reputational harm, our product candidate being considered misbranded and subject to relevant enforcement action, invalidation of the marketing application, and/or financial penalties. Our collaborators are also subject to similar requirements outside of the U.S. and the EU and thus the attendant risks and uncertainties.

In addition, we could be adversely affected by several significant administrative law cases decided by the U.S. Supreme Court in 2024. In Loper Bright Enterprises v. Raimondo, for example, the court overruled Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., which for 40 years required federal courts to defer to permissible agency interpretations of statutes that are silent or ambiguous on a particular topic. The U.S. Supreme Court stripped federal agencies of this presumptive deference and held that courts must exercise their independent judgment when deciding whether an agency such as the FDA acted within its statutory authority under the Administrative Procedure Act (the "APA"). Additionally, in Corner Post, Inc. v. Board of Governors of the Federal Reserve System, the court held that actions to challenge a federal regulation under the APA can be initiated within six years of the date of injury to the plaintiff, rather than the date the rule is finalized. The decision appears to give prospective plaintiffs a personal statute of limitations to challenge longstanding agency regulations. Another decision, Securities and Exchange Commission v. Jarkesy,

overturned regulatory agencies' ability to impose civil penalties in administrative proceedings. These decisions could introduce additional uncertainty into the regulatory process and may result in additional legal challenges to actions taken by federal regulatory agencies, including the FDA and the Centers for Medicare & Medicaid Services ("CMS"), that we rely on. In addition to potential changes to regulations as a result of legal challenges, these decisions may result in increased regulatory uncertainty and delays and other impacts, any of which could adversely impact our business and operations.

Our ability to develop and market new drug products may also be impacted by litigation challenging the FDA's approval of another company's drug product. In April 2023, the U.S. District Court for the Northern District of Texas invalidated the approval by the FDA of mifepristone, a drug product which was originally approved in 2000 and whose distribution is governed by various measures adopted under a REMS. The Court of Appeals for the Fifth Circuit declined to order the removal of mifepristone from the market but did hold that plaintiffs were likely to prevail in their claim that changes allowing for expanded access of mifepristone, which the FDA authorized in 2016 and 2021, were arbitrary and capricious. In June 2024, the Supreme Court reversed that decision after unanimously finding that the plaintiffs (anti-abortion doctors and organizations) did not have standing to bring this legal action against the FDA. On October 11, 2024, the Attorneys General of three states (Missouri, Idaho and Kansas) filed an amended complaint in the district court in Texas challenging FDA's actions. On January 16, 2025, the District Court agreed to allow these states to file an amended complaint and continue to pursue this challenge. Depending on the outcome of this litigation, our ability to develop new drug product candidates and to maintain approval of existing drug products could be delayed, undermined or subject to protracted litigation.

Finally, with the change in presidential administrations in 2025, there is substantial uncertainty as to how, if at all, the new administration will seek to modify or revise the requirements and policies of the FDA and other regulatory agencies with jurisdiction over our product candidates. The impending uncertainty could present new challenges or potential opportunities as we navigate the clinical development and approval process for our product candidates.

The approval of our and our collaborators' current or future product candidates for commercial sale could be delayed, limited or denied or we or they may be required to conduct additional studies for a number of reasons, including, but not limited to, the following:

- regulatory authorities may determine that our or our collaborators' product candidates do not demonstrate safety and effectiveness in accordance with regulatory agency standards based on a number of considerations, including AEs that are reported during clinical trials;
- regulatory authorities could analyze and/or interpret data from clinical trials and preclinical testing in different ways than we, or our collaborators, interpret them and determine that our data is insufficient for approval;
- regulatory authorities may require more information, including additional preclinical or clinical data or trials, to support approval, as in the case of our initiation of the EC-042 Study for patients with *TP53* wild-type advanced or recurrent endometrial cancer following discussions with the FDA in early 2022 on our SIENDO trial;
- regulatory authorities could determine that our manufacturing processes are not properly designed, are not conducted in accordance with federal or other laws or otherwise not properly managed, and we may be unable to obtain regulatory approval for a commercially viable manufacturing process for our product candidates in a timely manner, or at all;
- the supply or quality of our or our collaborators' product candidates for our clinical trials may be insufficient, inadequate or delayed;
- the size of the patient population required to establish the effectiveness of our or our collaborators' product candidates to the satisfaction of regulatory agencies may be larger than we or they anticipated;
- our failure or the failure of clinical investigational sites and the records kept at the respective locations, including clinical trial data, to be in compliance with the FDA's current good clinical practices regulations ("GCP") or comparable regulations outside of the U.S., including the failure to pass inspections of our corporate site or our clinical trial sites;
- regulatory authorities may change their approval policies or adopt new regulations;
- regulatory authorities may not be able to undertake reviews, applicable inspections or approval processes in a timely manner;
- the results of our earlier clinical trials may not be representative of our future, larger trials;

- regulatory authorities may not agree with our or our collaborators' regulatory approval strategies or components of our or their regulatory filings, such as the design or implementation of the relevant clinical trials; for example, the FDA identified multiple risks related to our decision to decrease the total number of patients to be enrolled in our ongoing Phase 3 multiple myeloma trial, including the ability to adequately assess benefit-risk with a limited number of patients; or
- a product may not be approved for the indications that we, or our collaborators, request or may be limited or subject to restrictions or post-approval commitments that render the approved drug not commercially viable.

As of January 1, 2025, a new international recognition procedure ("IRP") will apply, which intends to facilitate approval of pharmaceutical products in the UK. The IRP is open to applicants that have already received an authorization for the same product from one of the MHRA's specified Reference Regulators ("RRs"). The RRs notably include EMA and regulators in the EU/European Economic Area ("EEA") member states for approvals in the EU centralized procedure and mutual recognition procedure as well as the FDA (for product approvals granted in the U.S.). However, the concrete functioning of the IRP is currently unclear. Any delay in obtaining, or an inability to obtain, any marketing approvals, may force us or our collaborators to restrict or delay efforts to seek regulatory approval in the UK for our product candidates, which could significantly and materially harm our business.

We, or our collaborators, may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our or their products in any market. Any failure, delay or setback in obtaining regulatory approval for our or our collaborators' product candidates could materially adversely affect our or our collaborators' ability to generate revenue from a particular product candidate, which could result in significant harm to our financial position and adversely impact our stock price.

We, or our collaborators, may seek approval from the FDA or comparable foreign regulatory authorities to use accelerated development pathways for our product candidates. If we, or our collaborators, are not able to use such pathways, we, or they, may be required to conduct additional clinical trials beyond those that are contemplated, which would increase the expense of obtaining, and delay the receipt of, necessary marketing approvals, if we, or they, receive them at all. In addition, even if an accelerated approval pathway is available to us, or our collaborators, it may not lead to expedited approval of our product candidates, or approval at all.

Under the Federal Food, Drug and Cosmetic Act ("FDCA") and implementing regulations, the FDA may grant accelerated approval to a product candidate to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies, upon a determination that the product 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 measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug. 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. Similar risks to those described above are also applicable to any application that we, or our collaborators, have submitted or may submit in other jurisdictions outside of the U.S. Prior to seeking such accelerated approval, we, or our collaborators, will continue to seek feedback from the FDA or comparable foreign regulatory agencies and otherwise evaluate our, or their, ability to seek and receive such accelerated approval.

There can be no assurance that the FDA or foreign regulatory agencies will agree with our, or our collaborators', surrogate endpoints or intermediate clinical endpoints in any of our, or their, clinical trials, or that we, or our collaborators, will decide to pursue or submit any additional New Drug Applications ("NDA") for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that, after feedback from the FDA or comparable foreign regulatory agencies, we, or our collaborators, will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval. Furthermore, for any submission of an application for accelerated approval or application under another expedited regulatory designation, there can be no assurance that such submission or application will be accepted for filing or that any expedited development, review or approval will be granted on a timely basis, or at all.

Finally, there can be no assurance that we will satisfy all FDA requirements, including new provisions, that govern accelerated approval. For example, with passage of the FDORA in December 2022, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded and to submit progress reports on its post-approval studies to FDA every six months until the study is completed. Moreover, FDORA established expedited procedures authorizing FDA to

withdraw an accelerated approval if certain conditions are met, including where a required confirmatory study fails to verify and describe the predicted clinical benefit or where evidence demonstrates the product is not shown to be safe or effective under the conditions of use. The FDA may also use such procedures to withdraw an accelerated approval if a sponsor fails to conduct any required post-approval study of the product with due diligence, including with respect to "conditions specified by the Secretary." The new procedures include the provision of due notice and an explanation for a proposed withdrawal, and opportunities for a meeting with the Commissioner or the Commissioner's designee and a written appeal, among other things. We will need to fully comply with these and other requirements in connection with the development and approval of any product candidate that qualifies for accelerated approval.

In March 2023, the FDA issued draft guidance that outlines its current thinking and approach to accelerated approval. The FDA indicated that the accelerated approval pathway is commonly used for approval of oncology drugs due to the serious and life-threatening nature of cancer. Although single-arm trials have been commonly used to support accelerated approval, a randomized controlled trial is the preferred approach as it provides a more robust efficacy and safety assessment and allows for direct comparisons to an available therapy. To that end, the FDA outlined considerations for designing, conducting, and analyzing data for trials intended to support accelerated approvals of oncology therapeutics. Subsequently, in December 2024, the FDA issued additional draft guidance relating to accelerated approval. These guidances describe FDA's latest thinking on what it means to conduct a confirmatory trial with due diligence and how the FDA plans to interpret whether such a study needs to be underway at the time of approval. While these guidances are currently only in draft form and will ultimately not be legally binding even when finalized, sponsors typically observe the FDA's guidance closely to ensure that their investigational products qualify for accelerated approval.

Accordingly, a failure to obtain and maintain accelerated approval or any other form of expedited development, review or approval for our product candidates, or withdrawal of a product candidate, would result in a longer time period until commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

XPOVIO and any of our product candidates for which we, or our collaborators, obtain marketing approval in the future are subject to post-marketing regulatory requirements, including following accelerated or conditional approvals of our product candidates, and could be subject to post-marketing restrictions or withdrawal from the market, and we, and our collaborators, may be subject to substantial penalties if we, or they, fail to comply with regulatory requirements or if we, or they, experience unanticipated problems with our products following approval.

Once marketing approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. XPOVIO and any of our product candidates for which we, or our collaborators, obtain marketing approval in the future, as well as the manufacturing processes, post-approval studies and measures, labeling, advertising and promotional activities for such drug, among other things, will be subject to continual requirements of and review by the FDA and other U.S. and foreign regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and record keeping. For example, as a condition of the XPOVIO accelerated approvals by the FDA for the multiple myeloma and DLBCL indications, we are required to complete certain post-marketing commitments. There is no assurance that we will be able to timely complete such obligations. Failure to comply with such requirements may have an adverse impact on the accelerated approval status of selinexor in DLBCL. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the drug may be marketed or to the conditions of approval, including the requirement to implement a REMS, which could include requirements for a restricted distribution system.

The FDA also imposes requirements for costly post-marketing studies or clinical trials to maintain approval of any products that received accelerated or conditional approval. For drugs approved under the FDA's Accelerated Approval Program, the FDA typically requires post-marketing confirmatory trials to evaluate the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence. For example, in June 2020, the FDA approved XPOVIO to treat DLBCL under the FDA's accelerated approval regulations and as a condition of the accelerated approval for this indication we are required to comply with a number of post-approval requirements. We may not be able to successfully and timely complete these post-approval requirements, obtain an extension, if needed, or complete any other post-marketing confirmatory study as required to maintain approval or achieve full approval of our products. If required post-approval studies fail to verify the clinical benefits of our products or confirm that the surrogate marker used for accelerated approval of our products showed an adequate correlation with clinical outcomes, if a sufficient number of participants cannot be enrolled, or if we fail to perform the required post-approval studies with due diligence or on a timely basis, the FDA has the authority to withdraw approval of the drug following a hearing conducted under the FDA's regulations, which could have a material adverse impact on our business. We cannot be certain of the results of the confirmatory clinical studies for the DLBCL indication or any other future conditional approval we receive or what action the FDA may take if the results of those studies are not as expected based on clinical data that FDA has already reviewed.

Similar risks to those described above are also applicable to any application that we, or our collaborators, have submitted or may submit in other jurisdictions outside of the U.S., including applications submitted to the EMA to support approval of selinexor to treat patients with multiple myeloma or any other cancer indication. For medicinal products where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in legislation and guidelines, it is possible to obtain a conditional marketing authorization for a new drug in the EU with a 12-month validity period and annual renewal pursuant to Regulation No 507/2006. These are granted only if the EMA's Committee for Medicinal Products for Human Use ("CHMP") finds that all four of the following requirements are met: (i) the benefit-risk balance of the product is positive; (ii) it is likely that the sponsor will be able to provide comprehensive data; (iii) unmet medical needs will be fulfilled; and (iv) the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to the need for further data.

Once a conditional marketing authorization has been granted, the marketing authorization holder must fulfill specific obligations within defined timelines. These obligations could include completing ongoing or new studies or collecting additional data to confirm the medicine's benefit-risk balance remains positive. For example, the July 2022 marketing authorization from the European Commission ("EC") for NEXPOVIO to treat adult patients with multiple myeloma after at least one prior therapy satisfied the conditional approval obligation for NEXPOVIO for patients with multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. Conditional marketing authorization is valid for a period of one year and can be renewed/prolonged if the conditions set out in the conditional marketing authorization are met. Further, as discussed above, under FDORA, modifications to regulations governing accelerated approval require a sponsor to have the confirmatory clinical trial underway before accelerated approval is awarded as well as other requirements following accelerated approval. If we, or our collaborators, are not able to fulfill the specific obligations set out in any conditional marketing authorization requirements, the conditional marketing authorization may not be prolonged and we, or our collaborators, will no longer be able to market the product for the indication receiving conditional approval.

The FDA and comparable foreign regulatory authorities may also impose requirements for costly surveillance to monitor the safety or efficacy of an approved drug. The FDA and other U.S. or foreign agencies, including the DOJ, closely regulate and monitor the post-approval marketing and promotion of drugs to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use, and if we, or our collaborators communicate about any of our product candidates for which we, or they, receive marketing approval in a way that regulators assert goes beyond their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing. Alleged violations of the FDCA or other statutes, including the False Claims Act (the "FCA"), relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws.

We will need to carefully navigate the FDA's various regulations, guidance and policies, along with recently enacted legislation, to ensure compliance with restrictions governing promotion of our products. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug or biologic. Moreover, with passage of the Pre-Approval Information Exchange Act in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. In addition, in October 2023, the FDA published draft guidance outlining the agency's non-binding policies governing the distribution of scientific information on unapproved uses to healthcare providers. This draft guidance calls for such communications to be truthful, non-misleading, factual, and unbiased and include all information necessary for healthcare providers to interpret the strengths and weaknesses and validity and utility of the information about the unapproved use. This guidance was finalized in January 2025.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive requirements by the FDA and comparable foreign regulatory authorities, including ensuring that quality control and manufacturing procedures conform to current Good Manufacturing Practice ("cGMP"), which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, our contract manufacturers, our collaborators and their contract manufacturers could be subject to periodic unannounced inspections by the FDA or foreign regulatory authorities to monitor and ensure compliance with cGMPs or other regulations.

Post-approval discovery of previously unknown problems with our products, including AEs of unanticipated severity or frequency, or relating to our manufacturing processes, data integrity issues with regulatory filings, or failure to comply with regulatory requirements, may yield various results, including:

- litigation involving patients taking our drug;

- restrictions on our manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of our products;
- restrictions on the distribution or use of our products;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal, recall or seizure of our products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with our current or potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products; or
- injunctions or the imposition of civil or criminal penalties.

Similar restrictions apply to the approval of our products in the EU. The holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- compliance with the EU's stringent pharmacovigilance or safety reporting rules, which can impose post-authorization studies and additional monitoring obligations;
- the manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the EC Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU; and
- the marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU notably under Directive 2001/83/EC, as amended, and are also subject to EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

Finally, we or our collaborators are also subject to other regulations in various jurisdictions, including the Drug Supply Chain Security Act (the "DSCSA") in the U.S., the Falsified Medicines Directive in the EU and similar laws and regulations in other countries that require us or them to develop electronic systems to serialize, track, trace and authenticate units of our products through the supply chain and distribution system. Compliance with these regulations may result in increased expenses for us or our collaborators or impose greater administrative burdens on our or their organizations, and any failure on our or our collaborators' part to meet these requirements could result in fines or other penalties or reputational harm.

Accordingly, in connection with our currently approved products and assuming we, or our collaborators, receive marketing approval for one or more of our product candidates, we, and our collaborators, and our and their contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we, and our collaborators, are not able to comply with post-approval regulatory requirements, our or our collaborators' ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

If we, or our collaborators, are required by the FDA, EMA or comparable regulatory authority to obtain clearance or approval of one or more companion diagnostic tests in connection with approval of any of our product candidates or a group of therapeutic products, and we or they do not obtain or there are delays in obtaining clearance or approval of a diagnostic test, we may not be able to commercialize the product candidate and our ability to generate revenue may be materially impaired.

In connection with our ongoing development of selinexor in patients whose endometrial cancer is *TP53* wild-type, we are utilizing a companion diagnostic to identify patients whose tumors are *TP53* wild-type. We may be required to develop a second companion diagnostic pending the ultimate patient population included in the potential label for our endometrial indication. To be successful in developing and commercializing product candidates in combination with companion diagnostics, we or our collaborators will need to address a number of scientific, technical, regulatory and logistical challenges. According to FDA guidance, if the FDA determines that a companion diagnostic device is essential to ensuring the safety and effectiveness of a novel therapeutic product or new indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared. In certain circumstances (for example, when a therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory available therapy exists or when the labelling of an approved product needs to be revised to address a serious safety issue), however, the FDA may approve a therapeutic product without the prior or contemporaneous marketing authorization of a companion diagnostic. In this case, approval of a companion diagnostic may be a post-marketing requirement or commitment.

If the FDA requires clearance or approval of a companion diagnostic for any of our product candidates, whether before, concurrently with approval, or post-approval of the product candidate, we, and/or our collaborators, may encounter difficulties in developing and obtaining clearance or approval for these companion diagnostics. The process of obtaining or creating such diagnostic is time consuming and costly. The FDA previously has required in vitro companion diagnostics intended to select the patients who will respond to a product candidate to obtain pre-market approval ("PMA"), simultaneously with approval of the therapeutic candidate.

The PMA process, including the gathering of clinical data and the submission and review by the FDA, can take several years or longer. It involves a rigorous pre-market review during which the sponsor must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing, and labeling. After a device is placed on the market, it remains subject to significant regulatory requirements, including requirements, such as the Quality Management System Regulation as part of 21 CFR 820, which governs development, testing, manufacturing, distribution, marketing, promotion, labeling, import, export, record-keeping, and adverse event reporting. Similar risks to those described above are also applicable to any companion diagnostic that we, or our collaborators, utilize in our clinical trials in connection with approval of a product candidate outside of the U.S. For example, in the EU, until May 25, 2022, in vitro diagnostic medical devices were regulated by Directive 98/79/EC (the "IVDD"), which has been repealed and replaced by Regulation (EU) No 2017/746 (the "IVDR"). The regulation of companion diagnostics is now subject to further requirements set forth in the IVDR. Companion diagnostics will have to undergo a conformity assessment by a notified body. Before it can issue an EU certificate, the notified body must seek a scientific opinion from the EMA on the suitability of the companion diagnostic to the medicinal product concerned if the medicinal product falls exclusively within the scope of the centralized procedure for the authorization of medicines, or the medicinal product is already authorized through the centralized procedure, or a marketing authorization application for the medicinal product has been submitted through the centralized procedure. As part of the process to obtain a CE-mark for the FMI FoundationOne®CDx for the purpose of determining *TP53* wild-type status for use of selinexor in the maintenance treatment of *TP53* wild-type endometrial cancer patients, a performance study is required which leverages our EC-042 Trial (e.g., using the unapproved FoundationOne®CDx IVD to screen for *TP53* wild-type patients in the EC-042 Trial and using the data generated to validate the CDx itself). As the regulations are relatively new, the industry is gaining experience in the compilation of these submissions while the national Competent Authorities and the respective Ethics Committees are also gaining expertise in assessing these applications. As a result, the assessment deadlines of these performance study submissions and amendments are often not met. These new regulations have and could continue to negatively impact the pace of enrollment in our clinical trials. For example, in 2023, site activation for our Phase 3 clinical trial in endometrial cancer was delayed in the EU due to the new IVDR regulations. Consequently, the ability to use the FoundationOne®CDx in vitro diagnostic medical devices to screen patients for *TP53* status in the EC-042 Trial has been delayed in various countries in the EU.

We may rely on third parties for the design, development and manufacture of companion diagnostic tests for our product candidates, such as in the case of our ongoing Phase 3 trial evaluating selinexor in patients with *TP53* wild-type advanced or recurrent endometrial cancer. If we enter into such collaborative agreements, we will be dependent on the sustained cooperation and effort of our future collaborators in developing and obtaining clearance or approval for these companion diagnostics. It may be necessary to resolve issues such as selectivity/specificity, analytical validation, reproducibility, or clinical validation of companion diagnostics during the development and regulatory clearance or approval processes. Moreover, even if data from preclinical studies and early clinical trials appear to support development of a companion diagnostic for a product candidate, data generated in later clinical trials may fail to support the analytical and clinical validation of the companion diagnostic. We and our future collaborators may encounter

difficulties in developing, obtaining regulatory clearance or approval for, manufacturing and commercializing companion diagnostics similar to those we face with respect to our product candidates themselves, including issues with achieving regulatory clearance or approval, production of sufficient quantities at commercial scale and with appropriate quality standards, and in gaining market acceptance.

If we are unable to successfully develop companion diagnostics for our product candidates, or experience delays in doing so, the development of our product candidates may be adversely affected, our product candidates may not obtain marketing approval, and we may not realize the full commercial potential of any of our product candidates that obtain marketing approval. As a result, our business, results of operations and financial condition could be materially harmed. In addition, a diagnostic company with whom we contract may decide to discontinue selling or manufacturing the companion diagnostic test that we anticipate using in connection with development and commercialization of product candidates or our relationship with such diagnostic company may otherwise terminate. We may not be able to enter into arrangements with another diagnostic company to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the co-development or commercialization of our companion diagnostic and therapeutic product candidates.

We or our collaborators may seek certain designations for our product candidates in or outside of the U.S., including Breakthrough Therapy, Fast Track and Priority Review designations, and PRIME Designation in the EU, but we, or they, might not receive such designations, and even if we, or they, do, such designations may not lead to a faster development or regulatory review or approval process.

We may seek certain designations for one or more of our product candidates that could expedite review and approval by the FDA. A Breakthrough Therapy product is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For products that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens.

The FDA may also designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective.

We may also seek a Priority Review designation for one or more of our product candidates. If the FDA determines that a product candidate would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A Priority Review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months.

These designations are within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for these designations, the FDA may disagree and instead determine not to make such designation. Further, even if we receive a designation, such as the receipt of Fast Track designation for selinexor to treat myelofibrosis, the receipt of such designation for a product candidate may not result in a faster development or regulatory review or approval process compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualifies for these designations, the FDA may later decide that the product candidates no longer meet the conditions for qualification and rescind the designation or decide that the time period for FDA review or approval will not be shortened.

In the EU, we or our collaborators may seek PRIME designation for some of our product candidates in the future. PRIME is a voluntary program aimed at enhancing the EMA's role to reinforce scientific and regulatory support in order to optimize development and enable accelerated assessment of new medicines that are of major public health interest with the potential to address unmet medical needs. The program focuses on medicines that target conditions for which there exists no satisfactory method of treatment in the EU or even if such a method exists, it may offer a major therapeutic advantage over existing treatments. PRIME is limited to medicines under development and not authorized in the EU and the sponsor intends to apply for an initial MAA through the centralized procedure. To be accepted for PRIME, a product candidate must meet the eligibility criteria with respect to its major public health interest and therapeutic innovation based on information that is capable of substantiating the claims. The benefits of a PRIME

designation include the appointment of a CHMP rapporteur to provide continued support and help to build knowledge ahead of a MAA, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME enables a sponsor to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if we or our collaborators receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of the EMA's grant of a marketing authorization.

We, or our collaborators, may not be able to obtain orphan drug exclusivity for any product candidates we, or they, may develop, and even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition. A similar regulatory scheme governs approval of orphan products by the EMA in the EU. Generally, if a product candidate with an Orphan Drug Designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA, as applicable, from approving another marketing application for the same product for the same therapeutic indication for that time period. The applicable period is seven years in the U.S. and ten years in the EU. The exclusivity period in the EU can be reduced to six years if a product no longer meets the criteria for Orphan Drug Designation, in particular if the product is sufficiently profitable so that market exclusivity is no longer justified.

In order for the FDA to grant orphan drug exclusivity to one of our products, the agency must find that the product is indicated for the treatment of a condition or disease with a patient population of fewer than 200,000 individuals annually in the U.S. The FDA may conclude that the condition or disease for which we seek orphan drug exclusivity does not meet this standard. Even if we obtain orphan drug exclusivity for a product, such as the recent receipt of orphan drug exclusivity for selinexor for the treatment of myelofibrosis, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. In addition, even after an orphan drug is approved, the FDA and comparable foreign regulatory authorities, such as the EMA, can subsequently approve the same product for the same condition if the FDA or such other authorities conclude that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of the patients with the rare disease or condition.

In 2017, the Congress passed the FDA Reauthorization Act of 2017 (the "FDARA"). The FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. Under omnibus legislation signed by former President Trump in December 2020, the requirement for a product to show clinical superiority applies to drugs and biologics that received Orphan Drug Designation before the enactment of the FDARA in 2017, but have not yet been approved or licensed by the FDA.

The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term "same disease or condition" means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved.

We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future or whether Congress will take legislative action, and it is uncertain how any changes might affect our business. Depending on what changes the FDA or Congress may make to orphan drug regulations and policies, our business could be adversely impacted.

Inadequate funding for the FDA, the SEC and other government agencies, including from government shut downs, or other disruptions to these agencies' operations, could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA 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. Average review times at the agency have fluctuated in recent years as a result. Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. 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.

In addition, disruptions may result from events similar to the COVID-19 pandemic. During the COVID-19 pandemic, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. In the event of a similar public health emergency in the future, the FDA may not be able to continue its current pace and review timelines could be extended. Regulatory authorities outside the U.S. facing similar circumstances may adopt similar restrictions or other policy measures in response to a similar public health emergency and may also experience delays in their regulatory activities.

Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, 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. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Current and future legislation may increase the difficulty and cost for us, or any collaborators, to obtain marketing approval and commercialize our or their product candidates, if approved, and affect the prices we, or they, may obtain.

In the U.S. and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our or our collaborators' product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell or commercialize XPOVIO or any product candidate for which we, or they, obtain marketing approval. We expect that current laws, 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, or any collaborators, may receive for any approved products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act (collectively the "PPACA"). In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031. The American Taxpayer Relief Act of 2012, 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. Further, with the passage of the Inflation Reduction Act (the "IRA") in August 2022, Congress extended the expansion of PPACA premium tax credits through 2025.

These and other laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our products or product candidates for which we may obtain regulatory approval or the frequency with which any such product is prescribed or used. For example, the Consolidated Appropriations Act, which was signed into law by President Biden in December 2022, made several changes to sequestration of the Medicare program. Section 1001 of the Act delays the 4% Statutory Pay-As-You-Go Act of 2010 sequester for two years, through the end of calendar year 2024. Triggered by enactment of the American Rescue Plan Act of 2021, the 4% cut to the Medicare program would have taken effect in January 2023. The Act's health care offset title includes Section 4163, which extends the 2% Budget Control Act of 2011 Medicare sequester for six months into fiscal year 2032 and lowers the payment reduction percentages in fiscal years 2030 and 2031.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with the enactment of the Tax Cuts and Jobs Act of 2017 (the "TCJA"), Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, in December 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the PPACA are invalid as well. In June 2021, the U.S. Supreme Court dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

In the EU, on December 13, 2021, Regulation No 2021/2282 on Health Technology Assessment ("HTA"), amending Directive 2011/24/EU, was adopted. While the Regulation entered into force in January 2022, it begins to apply from January 2025 onwards. The Regulation will have a phased implementation depending on the concerned products. The Regulation intends to boost cooperation among EU member states in assessing health technologies, including new medicinal products as well as certain high-risk medical devices, and provide the basis for cooperation at the EU level for joint clinical assessments in these areas. It will permit EU member states to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the highest potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria and new payment methodologies that govern XPOVIO or any other approved product and/or the level of reimbursement physicians receive for administering XPOVIO or any other approved product we, or our collaborators, might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from XPOVIO or from product candidates for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

The prices of prescription pharmaceuticals in the U.S. and foreign jurisdictions are subject to considerable legislative and executive actions and could impact the prices we obtain for our products, if and when licensed.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the U.S. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, former President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, the Department of Health and Human Services (the "HHS") and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program to import certain prescription drugs from Canada into the U.S. That regulation was challenged in a lawsuit by the Pharmaceutical Research and Manufacturers of America ("PhRMA") but the case was dismissed by a federal district court in February 2023 after the court found that PhRMA did not have standing to sue the

HHS. Seven states (Colorado, Florida, Maine, New Hampshire, New Mexico, Texas and Vermont) have passed laws allowing for the importation of drugs from Canada. North Dakota and Virginia have passed legislation establishing workgroups to examine the impact of a state importation program. As of October 2024, five states (Colorado, Florida, Maine, New Hampshire and New Mexico) had submitted Section 804 Importation Program proposals to the FDA. Vermont has submitted a concept letter to the HHS. On January 5, 2024, the FDA approved Florida's plan for Canadian drug importation. That state now has authority to import certain drugs from Canada for a period of two years once certain conditions are met. Florida will first need to submit a pre-import request for each drug selected for importation, which must be approved by the FDA. The state will also need to relabel the drugs and perform quality testing of the products to meet FDA standards.

Further, in November 2020, the HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers. The final rule would also eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and pharmacy benefit manager service fees. It originally was set to go into effect on January 1, 2022, but with passage of the IRA has been delayed by Congress to January 1, 2032.

On August 16, 2022, the IRA was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least nine years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. The first cycle of negotiations for the Medicare Drug Price Negotiation Program commenced in the summer of 2023. On August 15, 2024, the HHS published the results of the first Medicare drug price negotiations for ten selected drugs that treat a range of conditions, including diabetes, chronic kidney disease, and rheumatoid arthritis. The prices of these ten drugs will become effective January 1, 2026. On October 2, 2024, in final guidance, CMS indicated that it would announce the selection of up to 15 additional drugs covered by Part D for the second cycle of negotiations by February 1, 2025. That announcement was made on January 17, 2025. This second cycle of negotiations with participating drug companies will occur during 2025, and any negotiated prices for this second set of drugs will be effective starting January 1, 2027.

On June 6, 2023, Merck & Co. filed a lawsuit against the HHS and CMS asserting that, among other things, the IRA's Drug Price Negotiation Program for Medicare constitutes an uncompensated taking in violation of the Fifth Amendment of the Constitution. Subsequently, a number of other parties, including the U.S. Chamber of Commerce (the "Chamber"), Bristol Myers Squibb Company, the PhRMA, Astellas, Novo Nordisk, Janssen Pharmaceuticals, Novartis, AstraZeneca and Boehringer Ingelheim, also filed lawsuits in various courts with similar constitutional claims against the HHS and CMS. There have been various decisions by the courts considering these cases since they were filed. The HHS has generally won the substantive disputes in these cases, and various federal district court judges have expressed skepticism regarding the merits of the legal arguments being pursued by the pharmaceutical industry. Certain of these cases are now on appeal and, on October 30, 2024, the Court of Appeals for the Third Circuit heard oral argument in three of these cases.

Accordingly, while it is currently unclear how the IRA will be effectuated, we cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

At the state level, individual states are increasingly aggressive in passing legislation and implementing 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, regional healthcare organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Finally, outside of the U.S., in some nations, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we, or our collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies.

These measures, as well as others adopted in the future, may result in additional downward pressure on the price that we receive for XPOVIO or any other approved product we or our collaborators might bring to market. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from XPOVIO or from product candidates that we, or our collaborators, may successfully develop and for which we, or they, may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

Our relationships with healthcare providers, physicians and third-party payers will be subject to applicable anti-kickback, fraud and abuse, and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare professionals, including but not limited to physicians, nurses, medical directors, hospitals, pharmacies, pharmacy benefit managers, group purchasing organizations, wholesalers, insurers, and all individuals employed by such entities (collectively, "HCPs"), may influence the recommendation and prescription of our approved products. Our arrangements with HCPs and others who have the ability to influence the recommendation and prescription of our products 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 market, sell and distribute our medicines for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward 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 federal and state healthcare programs such as Medicare and Medicaid;
- the FCA imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting or causing to be presented, to the federal government, claims for payment or approval from Medicare, Medicaid or other government payers that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties;
- the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), as further amended by the Health Information Technology for Economic and Clinical Health Act, which imposes certain requirements, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, healthcare clearinghouses and healthcare providers;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the federal transparency requirements under the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies to report to the HHS, information related to payments and other transfers of value to physicians, other healthcare providers and teaching hospitals and ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations; and

- analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payers, including private insurers, and certain state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, imprisonment and the curtailment or restructuring of our operations, any of which could adversely affect our business, financial condition, results of operations and prospects.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve 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 civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are 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. Liabilities they incur pursuant to these laws could result in significant costs or an interruption in operations, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our reporting and payment obligations under the Medicaid Drug Rebate Program and other governmental drug pricing programs are complex and may involve subjective decisions. Any failure to comply with those obligations could subject us to penalties and sanctions.

As a condition of reimbursement by various federal and state health insurance programs, we are required to calculate and report certain pricing information to federal and state agencies. The regulations governing the calculations, price reporting and payment obligations are complex and subject to interpretation by various government and regulatory agencies, as well as the courts. Reasonable assumptions have been made where there is lack of regulations or clear guidance and such assumptions involve subjective decisions and estimates. We are required to report any revisions to our calculation, price reporting and payment obligations previously reported or paid. Such revisions could affect our liability to federal and state payers and also adversely impact our reported financial results of operations in the period of such restatement. Further, a number of states have either implemented or are considering implementation of drug price transparency legislation that may prevent or limit our ability to take price increases at certain rates or frequencies. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers for the untimely, inaccurate, or incomplete reporting of drug pricing information or for otherwise failing to comply with drug price transparency requirements. If we are found to have violated state law requirements, we may become subject to significant penalties or other enforcement mechanisms, which could have a material adverse effect on our business.

Uncertainty exists as new laws, regulations, judicial decisions, or new interpretations of existing laws, or regulations related to our calculations, price reporting or payments obligations increases the chances of a legal challenge, restatement or investigation. If we become subject to investigations, restatements, or other inquiries concerning our compliance with price reporting laws and regulations, we could be required to pay or be subject to additional reimbursements, penalties, sanctions or fines, which could have a material adverse effect on our business, financial condition and results of operations. In addition, it is possible that future healthcare reform measures could be adopted, which could result in increased pressure on pricing and reimbursement of our products and thus have an adverse impact on our financial position or business operations.

Further, state Medicaid programs may be slow to invoice pharmaceutical companies for calculated rebates resulting in a lag between the time a sale is recorded and the time the rebate is paid. This results in us having to carry a liability on our consolidated balance sheets for the estimate of rebate claims expected for Medicaid patients. If actual claims are higher than current estimates, our financial position and results of operations could be adversely affected.

In addition to retroactive rebates and the potential for 340B Program refunds, if we are found to have knowingly submitted any false price information related to the Medicaid Drug Rebate Program to CMS, we may be liable for civil monetary penalties. Such failure could also be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we participate in the Medicaid program. In the event that CMS terminates our rebate agreement, federal payments may not be available under government programs, including Medicaid or Medicare Part B, for our covered outpatient drugs.

Additionally, if we overcharge the government in connection with the Federal Supply Schedule pricing program or Tricare Retail Pharmacy Program, whether due to a misstated Federal Ceiling Price or otherwise, we are required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the FCA and other laws and regulations. Unexpected refunds to the government, and responding to a government investigation or enforcement action, would be expensive and time consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Our collaborators are also subject to similar requirements outside of the U.S. and thus the attendant risks and uncertainties. If our collaborators suffer material and adverse effects from such risks and uncertainties, our rights and benefits for our licensed products could be negatively impacted, which could have a material and adverse impact on our revenues.

We are subject to stringent privacy laws, information security laws, regulations, policies and contractual obligations related to data privacy and security and changes in such laws, regulations, policies and contractual obligations, and failure to comply with such requirements could subject us to significant fines and penalties and other consequences, which may have a material adverse effect on our business, financial condition or results of operations.

We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally-identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information, including comprehensive regulatory systems in the U.S., EU, UK and other countries in which we may conduct business. The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, imprisonment of company officials and public censure, claims for damages by affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects.

There are numerous U.S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation.

If we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In recent months, the Officer of Civil Rights ("OCR") has been especially active in enforcing the HIPAA rules. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems. Additionally, OCR is looking to amend the HIPAA Security Rule, which (if and when finalized) could create additional compliance obligations and risk for our business.

In addition to potential enforcement by the HHS, we could also be potentially subject to privacy enforcement from the Federal Trade Commission (the "FTC"). The FTC has been particularly focused on the unpermitted processing of health and genetic data through its recent enforcement actions and is expanding the types of privacy violations that it interprets to be "unfair" under Section 5 of the FTC Act, as well as the types of activities it views to trigger the Health Breach Notification Rule (which the FTC also has the authority to enforce). The agency is also in the process of developing rules related to commercial surveillance and data security. We will need to account for the FTC's evolving rules and guidance for proper privacy and data security practices in order to mitigate risk for a potential enforcement action, which may be costly. Finally, both the FTC and HHS's enforcement priorities (as well as those of other federal regulators) may be impacted by the change in administration and new leadership. These shifts in enforcement priorities may also impact our business.

There are also increased restrictions at the federal level relating to transferring sensitive data outside of the U.S. to certain foreign countries. For example, in 2024, Congress passed H.B. 815, which included the Protecting Americans' Data from Foreign Adversaries Act of 2024. This law creates certain restrictions for entities that disclose sensitive data (including potential health data) to countries such as China. Failure to comply with these rules can lead to a potential FTC enforcement action. Additionally, the Department of Justice recently finalized a rule implementing Executive Order 14117, which creates similar restrictions related to the transfer of sensitive US data to countries such as China. These data transfer restrictions (and others that may pass in the future) may create operational challenges and legal risks for our business.

States are also active in creating specific rules relating to the processing of personal information. In 2018, California passed into law the California Consumer Privacy Act (the "CCPA"), which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the European General Data Protection Regulation (the "GDPR"), which is further described below, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements.

In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act (the "CPRA"), which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – the sole responsibility of which is to enforce the CPRA and other California privacy laws, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities.

In addition to California, at least eighteen other states have passed comprehensive privacy laws similar to the CCPA and CPRA. These laws are either in effect or will go into effect over the next few years. Like the CCPA and CPRA, these laws create obligations related to the processing of personal information, as well as special obligations for the processing of "sensitive" data, which includes health data in some cases. Some of the provisions of these laws may apply to our business activities. There are also states that are strongly considering or have already passed comprehensive privacy laws during the 2024 legislative sessions that will go into effect in 2025 and beyond, including New Hampshire and New Jersey. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. There are also states that are specifically regulating health information that may affect our business. For example, Washington state passed a health privacy law in 2023 that regulates the collection and sharing of health information, and the law also has a private right of action, which further increases the relevant compliance risk. Connecticut and Nevada have also passed similar laws regulating consumer health data, and more states are considering such legislation in 2025. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Plaintiffs' lawyers are also increasingly using privacy-related statutes at both the state and federal level to bring lawsuits against companies for their data-related practices. In particular, there have been a significant number of cases filed against companies for their use of pixels and other web trackers. These cases often allege violations of the California Invasion of Privacy Act and other state laws regulating wiretapping, as well as the federal Video Privacy Protection Act. The rise in these types of lawsuits creates potential risk for our business.

Similar to the laws in the U.S., there are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area ("EEA"), and the processing of personal data that takes place in the EEA, is regulated by the GDPR, which went into effect in May 2018 and which imposes obligations on companies that operate in our industry with respect to the processing of personal data and the cross-border transfer of such data. The GDPR imposes onerous accountability obligations requiring data controllers and processors to maintain a record of their data processing and policies. If our or our partners' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the group of companies of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill.

The GDPR places restrictions on the cross-border transfer of personal data from the EU to countries that have not been found by the EC to offer adequate data protection legislation. There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the EU (the "CJEU") invalidated the EU-U.S. Privacy Shield,

one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U.S. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for international transfers of personal data from the EEA. This CJEU decision resulted in increased scrutiny on data transfers and increased our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

In October 2022, President Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which serves as a replacement to the EU-U.S. Privacy Shield. The EC adopted the adequacy decision on July 10, 2023. The adequacy decision permits U.S. companies who self-certify to the EU-U.S. Data Privacy Framework to rely on it as a valid data transfer mechanism for data transfers from the EU to the U.S. However, some privacy advocacy groups have already suggested that they will be challenging the EU-U.S. Data Privacy Framework. If these challenges are successful, they may not only impact the EU-U.S. Data Privacy Framework, but also further limit the viability of the standard contractual clauses and other data transfer mechanisms. The uncertainty around this issue has the potential to impact our business. Following the withdrawal of the UK from the EU, the UK Data Protection Act 2018 applies to the processing of personal data that takes place in the UK and includes parallel obligations to those set forth by GDPR. In relation to data transfers, both the UK and the EU have determined, through separate "adequacy" decisions, that data transfers between the two jurisdictions are in compliance with the UK Data Protection Act and the GDPR, respectively. The UK and the U.S. have also agreed to a U.S.-UK "Data Bridge", which functions similarly to the EU-U.S. Data Privacy Framework and provides an additional legal mechanism for companies to transfer data from the UK to the U.S.

Switzerland has also approved an adequacy decision in relation to the Swiss-U.S. Data Privacy Framework (which functions similarly to the EU-U.S. Data Privacy Framework and the U.S.-UK Data Bridge in relation to data transfers from Switzerland to the U.S.). Any changes or updates to these developments have the potential to impact our business.

Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and the sale and distribution of commercial products, through increased compliance costs, costs associated with contracting and potential enforcement actions.

While we continue to address the implications of the recent changes to data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges, and our efforts to comply with the evolving data protection rules may be unsuccessful. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the EEA and elsewhere and carries with it the potential for significant penalties if we are found to be non-compliant. Similarly, failure to comply with federal and state laws in the U.S. regarding privacy and security of personal information could expose us to penalties under such laws. Any such failure to comply with data protection and privacy laws could result in government-imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our business, financial condition, results of operations or prospects.

Our employees, independent contractors, consultants, collaborators and vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and/or requirements and insider trading, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, consultants, collaborators and vendors. Misconduct by these partners could include intentional, reckless and/or negligent conduct or unauthorized activities that violate FDA regulations or similar regulations of comparable foreign regulatory authorities; provide inaccurate information to the FDA or comparable foreign regulatory authorities; fail to comply with manufacturing standards, federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities; fail to comply with state drug pricing transparency filing requirements; fail to report financial information or data accurately; or fail to disclose unauthorized activities to us. Employee misconduct 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. This could include violations of HIPAA, other U.S. federal and state laws, and requirements of foreign jurisdictions, including the GDPR. We are also exposed to risks in connection with any insider trading violations by employees or others affiliated with us. It is not always possible to identify and deter employee or third-party misconduct, and the precautions we take to detect and prevent these activities may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from significant penalties, governmental investigations or other

actions or lawsuits stemming from a failure to be in compliance with such laws, standards, regulations, guidance or codes of conduct. 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 and results of operations, including the imposition of significant fines or other sanctions.

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 have a material adverse effect on our business.

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 and radioactive materials. Our operations and the operations of our third-party vendors 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 biological, hazardous or radioactive 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.

Laws and regulations governing international operations we may have in the future may preclude us from developing, manufacturing and selling certain products outside of the U.S. and require us to develop and implement costly compliance programs.

We are subject to numerous laws and regulations in each jurisdiction outside of the U.S. in which we operate. The creation, implementation and maintenance of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

The FCPA prohibits any U.S. individual or business from paying, offering, 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 U.S. to comply with certain accounting provisions requiring us 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. The FCPA is enforced by the DOJ and the SEC.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals, clinics, universities and similar institutions are operated by the government, and doctors and other healthcare professionals are considered foreign officials. Certain payments to healthcare professionals in connection with clinical trials, regulatory approvals, sales and marketing, and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions. Because the FCPA applies to indirect payments, the use of third parties and other collaborators can increase potential FCPA risk, as we could be held liable for the acts of third parties that do not comply with the FCPA's requirements.

The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violation of the FCPA can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

Like the FCPA, the UK Bribery Act and other anti-corruption laws throughout the world similarly prohibit offers and payments made to obtain improper business advantages, including offers or payments to healthcare professionals and other government and non-government officials. These other anti-corruption laws also can result in substantial financial penalties and other collateral consequences.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the U.S., or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Our expansion outside of the U.S., has required, and will continue to require, us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain drugs and product candidates outside of the U.S., which could limit our growth potential and increase our development costs.

With the passage of the CREATES Act, we are exposed to possible litigation and damages by competitors who may claim that we are not providing sufficient quantities of our approved products on commercially reasonable, market-based terms for testing in support of their ANDAs and 505(b)(2) applications.

In December 2019, former President Trump signed legislation intended to facilitate the development of generic and biosimilar products. The bill, previously known as the CREATES Act, authorizes sponsors of abbreviated new drug applications ("ANDAs") and 505(b)(2) applications to file lawsuits against companies holding NDAs that decline to provide sufficient quantities of an approved reference drug on commercially reasonable, market-based terms. Drug products on the FDA's drug shortage list are exempt from these new provisions unless the product has been on the list for more than six continuous months or the FDA determines that the supply of the product will help alleviate or prevent a shortage.

To bring an action under the statute, an ANDA or 505(b)(2) sponsor must take certain steps to request the reference product, which, in the case of products covered by a REMS with elements to assure safe use, include obtaining authorization from the FDA for the acquisition of the reference product. If the sponsor does bring an action for failure to provide a reference product, there are certain affirmative defenses available to the NDA holder, which must be shown by a preponderance of evidence. If the sponsor prevails in litigation, it is entitled to a court order directing the NDA holder to provide, without delay, sufficient quantities of the applicable product on commercially reasonable, market-based terms, plus reasonable attorney fees and costs.

Additionally, the new statutory provisions authorize a federal court to award the product developer an amount "sufficient to deter" the NDA holder from refusing to provide sufficient product quantities on commercially reasonable, market-based terms if the court finds, by a preponderance of the evidence, that the NDA holder did not have a legitimate business justification to delay providing the product or failed to comply with the court's order. For the purposes of the statute, the term "commercially reasonable, market-based terms" is defined as (1) the nondiscriminatory price at or below the most recent wholesale acquisition cost for the product, (2) a delivery schedule that meets the statutorily defined timetable, and (3) no additional conditions on the sale.

Although we intend to comply fully with the terms of these statutory provisions, we are still exposed to potential litigation and damages by competitors who may claim that we are not providing sufficient quantities of our approved products on commercially reasonable, market-based terms for testing in support of ANDAs and 505(b)(2) applications. Such litigation would subject us to additional litigation costs, damages and reputational harm, which could lead to lower revenues. The CREATES Act may enable generic competition with XPOVIO and any of our product candidates, if approved, which could impact our ability to maximize product revenue. In September 2022, the FDA issued draft guidance outlining certain of the provisions under this statute.

We are subject to governmental export and import controls that could impair our or our collaborators' ability to compete in international markets due to licensing requirements and subject us or them to liability if we or they are not in compliance with applicable laws.

Our products are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, and various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls. Exports of our products outside of the U.S. must be made in compliance with these laws and regulations. If we or our collaborators fail to comply with these laws and regulations, we or they and certain of our or their employees could be subject to substantial civil or criminal penalties, including the possible loss of export or import privileges; fines, which may be imposed on us or our collaborators and the respective responsible employees or managers; and, in extreme cases, the incarceration of responsible employees or managers.

In addition, changes in our products or changes in applicable export or import laws and regulations may create delays in the introduction, provision, or sale of our products in international markets, prevent customers from using our products or, in some cases, prevent the export or import of our products to certain countries, governments or persons altogether. Any limitation on our ability to export, provide, or sell our products could adversely affect our business, financial condition and results of operations.

Changes in U.S. and international trade policies, particularly with respect to China, may adversely impact our business and operating results.

The U.S. government has recently made statements and taken certain actions that may lead to potential changes to U.S. and international trade policies, including imposing several rounds of tariffs and export control restrictions affecting certain products manufactured in China. In March 2018, the Trump administration announced the imposition of tariffs on steel and aluminum entering the U.S. and in June 2018, the Trump administration announced further tariffs targeting goods imported from China. Recently both China and the U.S. have each imposed tariffs indicating the potential for further trade barriers, including the U.S. Commerce Department adding numerous Chinese entities to its "unverified list," which requires U.S. exporters to go through more procedures before exporting goods to such entities. It is unknown whether and to what extent new tariffs, export controls, or other new laws or regulations will be adopted, or the effect that any such actions would have on us or our industry.

Further, some of our raw material manufacturers and suppliers are located in China. Trade tensions and conflicts between the U.S. and China have been escalating in recent years and, as such, we are exposed to the possibility of product supply disruption and increased costs and expenses in the event of changes to the laws, rules, regulations and policies of the governments of the U.S. or China, or due to geopolitical unrest and unstable economic conditions. Certain Chinese biotechnology companies may become subject to trade restrictions, sanctions, other regulatory requirements or proposed legislation by the U.S. government, which could restrict or even prohibit our ability to work with such entities, thereby potentially disrupting their supply of material to us. For example, in February 2024, U.S. lawmakers called for investigations into and the imposition of possible economic sanctions against Chinese biotechnology companies WuXi AppTec and WuXi Biologics (collectively "WuXi") over alleged ties to the Chinese military. In addition, the recently proposed BIOSECURE Act introduced in the House of Representatives, as well as a substantially similar bill in the Senate, targets certain Chinese biotechnology companies. If these bills become law, or similar laws are passed, they would have the potential to severely restrict the ability of companies to contract with certain Chinese biotechnology companies of concern without losing the ability to contract with, or otherwise received funding from, the U.S. government. Such disruptions could have adverse effects on the development of our products or product candidates and our business operations.

Any unfavorable government policies on international trade, such as export controls, capital controls or tariffs, may increase the cost of manufacturing our product candidates and platform materials, affect the demand for our drug products (if and once approved), the competitive position of our product candidates, and import or export of raw materials and finished product candidate used in our and our collaborators' preclinical studies and clinical trials, particularly with respect to any product candidates and materials that we import from China. If any new tariffs, export controls, legislation and/or regulations are implemented, or if existing trade agreements are renegotiated or, in particular, if either the U.S. or Chinese government takes retaliatory trade actions due to the recent trade tension, such changes could have an adverse effect on our business, financial condition and results of operations.

Risks Related to Our Financial Position and Capital Requirements

Our financial condition raises substantial doubt as to our ability to continue as a going concern.

We will require substantial funds to maintain our research and development programs, including as we continue to develop and seek regulatory approval of selinexor for multiple cancer indications, and to support our continued operations. We have incurred significant operating losses since our inception. As of December 31, 2024, we had approximately $108.7 million in cash, cash equivalents and investments and an accumulated deficit of $1.6 billion. We anticipate that we will continue to incur significant operating losses as we continue to develop and seek regulatory approval of selinexor for multiple cancer indications. As a result, our continued operations are dependent on our ability to raise additional funding and marketing XPOVIO in its currently approved indications.

We plan to address the conditions that raise substantial doubt regarding our ability to continue as a going concern by, among other things, obtaining additional funding through equity offerings, debt financings and refinancings, collaborations, strategic alliances and/or licensing arrangements. However, there is no assurance that such additional funding will be available on terms acceptable to us or at all. We may also be required to reduce our current spending requirements where possible.

If we utilize our capital resources more quickly than anticipated or are unable to obtain additional funding, we may have to significantly curtail, delay, reduce or eliminate one or more of our research and development programs or any current or future commercialization efforts for one or more of our products or product candidates, which could materially adversely affect our business,

financial condition, and results of operations. If we are unable to continue as a going concern, we may have to liquidate our assets and may receive less than the value at which those assets are carried on our financial statements, and it is likely that investors will lose all or part of their investment. If we seek additional financing to fund our business activities in the future and there remains substantial doubt about our ability to continue as a going concern, investors or other financing sources may be unwilling to provide funding to us on commercially reasonable terms, if at all.

We have incurred significant losses since inception, expect to continue to incur significant losses, and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was $76.4 million for the year ended December 31, 2024. As of December 31, 2024, we had an accumulated deficit of $1.6 billion. As described above in "Our financial condition raises substantial doubt as to our ability to continue as a going concern," our financial condition raises substantial doubt about our ability to continue as a going concern. Although we received our first FDA-approval for XPOVIO in July 2019, we may never attain profitability or positive cash flows from operations. We have historically financed our operations primarily through a combination of proceeds from (i) product revenue sales, (ii) public and private placements of equity securities, (iii) the issuance of convertible debt, (iv) a term loan, (v) our deferred royalty obligation, (vi) at the market offerings and (vii) business development activities. Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs, the pursuit of regulatory approvals within and outside of the U.S., and the commercialization of XPOVIO. We expect to continue to incur significant expenses and operating losses as we continue to commercialize XPOVIO in the U.S. and engage in activities to prepare for the potential approval and commercialization of additional indications for selinexor as well as any other product candidates we develop or acquire. The net losses we incur may fluctuate significantly from quarter to quarter.

While we began to generate revenue from the sales of XPOVIO in July 2019 and have received revenue from our license arrangements, such as the partnership we have with Antengene Therapeutics Limited ("Antengene") for our programs across most of the Asia-Pacific region, and with Menarini for our programs in Europe, Latin America, certain Middle East and Africa regions and other key countries, there can be no assurance as to the amount or timing of future product or license and other revenues, and we may not achieve profitability for several years, if at all. Our ability to become and remain profitable depends significantly on our success in many areas, including:

- effectively commercializing XPOVIO or any future products either on our own or with a collaborator, including by maintaining a full commercial organization required to market, sell and distribute our products, and achieving an adequate level of market acceptance;
- the impact of current or future competing products on product sales of XPOVIO or any of our future products;
- obtaining sufficient pricing, coverage and reimbursement, including government pricing and reimbursement policies or a change in the mix of our business effecting rebates related to 340B Programs, Medicare and Medicaid, for XPOVIO and any of our other approved products from private and government payers and the impact of any pricing changes, any of which can impact our gross-to-net provisions related to product sales;
- initiating and successfully completing clinical trials required to file for, obtain and maintain marketing approval for our product candidates;
- obtaining and maintaining regulatory approvals, either by us or our collaborators, and the timing of such approvals;
- manufacturing at commercial scale;
- establishing and managing any collaborations for the development, marketing and/or commercialization of our products and product candidates, including the level of success of our collaborators' efforts and the timing and amount of any milestone or royalty payments we may receive;
- obtaining, maintaining and protecting our intellectual property rights;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage or as co-pay amounts under third-party coverage; for example, multiple myeloma foundation closures during 2023 resulted in significantly increased use of our PAP, which adversely impacted our 2023 revenues; and
- navigating the negative impacts to healthcare systems, the ability of our clinical trial sites to conduct current or future trials and the regulatory review process as the result of pandemics or other public health emergencies.

We anticipate that our operating expenses will continue to be significant and increase as we continue to:

- commercialize XPOVIO in the U.S., including maintaining our commercial infrastructure, and engage in activities to prepare for the potential approval and commercialization of additional indications for selinexor;
- obtain and/or maintain regulatory approval for XPOVIO and our product candidates, including completing any required post-marketing requirements to the satisfaction of the FDA or other regulatory agencies;
- expand our research and development programs, identify additional product candidates and initiate and conduct clinical trials, including clinical trials required by the FDA or other regulatory agencies in addition to those that have been or are currently expected to be conducted;
- maintain, expand and protect our intellectual property portfolio;
- manufacture XPOVIO and our product candidates; and
- acquire or in-license other products, product candidates or technologies.

Because of the numerous risks and uncertainties associated with pharmaceutical product development and commercialization, we are unable to accurately predict the timing or amount of our revenue and expenses or when, or if, we will be able to achieve profitability. We cannot be certain that our revenue from sales of XPOVIO alone, in the currently approved indications, will be sufficient for us to become profitable for several years, if at all. We may never generate revenues that are significant or large enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development and commercialization efforts, expand our business and/or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

We will need additional funding to achieve our business objectives. If we are unable to raise capital when needed or on acceptable terms, we would be forced to delay, reduce or eliminate our research and development programs and/or commercialization efforts.

Discovering, developing and commercializing products involve time-consuming, expensive and uncertain processes that take years to complete. We have used substantial funds to develop XPOVIO and expect our operating expenses to continue to increase as we continue to commercialize XPOVIO or any future approved product, conduct further research and development of our product candidates, seek marketing approval and prepare for commercialization of selinexor in additional indications or for our other product candidates, if approved, to the extent that such functions are not the responsibility of a collaborator. Furthermore, we will continue to incur additional costs associated with operating as a public company, hiring additional personnel and expanding our geographical reach. Although currently XPOVIO is commercially available in three indications, we do not anticipate that our revenue from product sales of XPOVIO or any funds we may receive from our collaborators will be sufficient for us to become profitable for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives.

As of December 31, 2024, we believe that our existing cash, cash equivalents and investments will enable us to fund our current operating plans and debt obligation requirements into the fourth quarter of 2025. The amount and timing of our future capital requirements will depend on many factors, including, but not limited to:

- the scope, progress, results, timing and costs of our current and planned development efforts and regulatory review of our product candidates;
- the amount and timing of revenues from sales of XPOVIO, or any product candidate that we develop or acquire;
- the cost of, and our ability to expand and maintain, the commercial infrastructure required to support the commercialization of XPOVIO and any other product for which we receive marketing approval, including medical affairs, manufacturing, marketing and distribution functions;
- our ability to establish and maintain collaboration, partnership, licensing, marketing, distribution or other arrangements on favorable terms and the level and timing of success of these arrangements, and our ability to use proceeds of those arrangements in our business as opposed to being required to pay those proceeds to the lenders of our $100.0 million senior secured term loan facility (the "Term Loan") and/or holders of the Convertible Senior Notes due 2025 (the "2025 Notes") and the secured Convertible Senior Notes due 2029 (the "2029 Notes");
- the extent to which we acquire or in-license other products, product candidates and technologies, and our ability to enter into such acquisitions and in-licenses pursuant to the restrictions under the Term Loan and the 2029 Notes;

- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and
- our ability to continue as a going concern.

In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. If we raise additional funds by issuing equity securities, dilution to our existing stockholders will result. In addition, as a condition to providing additional funding to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Moreover, in addition to the restrictions on our operations under the Term Loan and the 2029 Notes, the restrictions contained in the Amended Revenue Interest Agreement (defined below) and the repayment requirements in respect of obligations from proceeds of the transactions under each of the foregoing agreements, any future debt financing, if available and permitted, may involve further restrictive covenants that could limit our flexibility in conducting future business activities and using transaction proceeds in our business and, in the event of insolvency, the Term Loan, the 2029 Notes, the 2025 Notes, the Amended Revenue Interest Agreement obligations, and any further indebtedness, if available and permitted, would be paid before holders of equity securities received any distribution of corporate assets. Our ability to satisfy and meet our current and any future debt service obligations will depend upon our future performance, which will be subject to financial, business and other factors affecting our operations, many of which are beyond our control.

Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital due to favorable market conditions or strategic considerations. Any future fundraising efforts could divert management's attention away from their day-to-day activities. Further, adequate additional financing may not be available to us on acceptable terms, or at all. In addition, raising funds in the current economic environment may present additional challenges. For example, any sustained disruption in the capital markets from adverse macroeconomic conditions, such as the disruption and uncertainty caused by inflation, sustained high interest rates and slower economic growth or recession, could negatively impact our ability to raise capital and we cannot predict the extent or duration of such macro-economic disruptions. Moreover, there has been turmoil in the global banking system, which could result in loss of or access to our deposits, and an inability to obtain financing from other sources. If adequate funds are not available to us on a timely basis or on attractive terms, we may be required to delay, reduce or eliminate our research and development programs or any current or future commercialization efforts for one or more of our products or product candidates, any of which could have a material adverse effect on our business, operating results and prospects.

Our Amended Revenue Interest Agreement with HCRx contains various covenants and other provisions, which, if violated, could, subject to the Intercreditor Agreement, result in the acceleration of payments due under such agreement or the foreclosure on the pledged collateral, including all of our present and future assets relating to selinexor.

In September 2019, we entered into the Revenue Interest Financing Agreement with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. (collectively, "HCRx"), which was amended in June 2021, August 2023 and May 2024 (the "Amended Revenue Interest Agreement"). Pursuant to the Amended Revenue Interest Agreement, we are required to comply with various covenants relating to the conduct of our business and the commercialization of XPOVIO, including obligations to use commercially reasonable efforts to commercialize our products. In addition, the Amended Revenue Interest Agreement limits our ability to incur or prepay indebtedness, create or incur liens, pay dividends on or repurchase outstanding shares of our capital stock or dispose of assets. The Amended Revenue Interest Agreement also includes customary events of default upon the occurrence of enumerated events, including non-payment of revenue interests, failure to perform certain covenants and the occurrence of insolvency proceedings, specified judgments, specified cross-defaults and specified revocations, withdrawals, suspensions or cancellations of regulatory approval for XPOVIO. Upon the occurrence of an event of default and in the event of a change of control, HCRx may accelerate payments due under the Amended Revenue Interest Agreement up to $128.3 million, less the aggregate amount of all of the payments paid to HCRx after the date of the May 2024 amendment. Our obligations to HCRx are secured by a second-priority security interest in certain assets of ours related to selinexor, which shares such second priority with the 2029 Notes and which is subordinated to the first-priority security interest securing the Term Loan. Subject to an intercreditor agreement with HCRx, the Term Loan lenders and the holders of the 2029 Notes (the "Intercreditor Agreement"), in the event that an uncured default by us under the Amended Revenue Interest Agreement results in an acceleration of obligations by HCRx which we are unable to pay, HCRx will have the right to foreclose on the collateral that was pledged to HCRx. Any such foreclosure remedy would significantly and adversely affect us and could result in us losing our interest in such assets, which would have a material adverse impact on our business.

Our Credit Agreement and indenture governing the 2029 Notes contain various covenants and other provisions, which will limit the manner in which we may operate, and, if violated, could, subject to the Intercreditor Agreement, result in the acceleration of payments due under such agreements or the foreclosure on the pledged collateral, including all of our present and future assets.

The May 2024 credit and guaranty agreement (the "Credit Agreement") and the indenture governing the 2029 Notes contain, and any future indebtedness that we incur may contain, various negative covenants that restrict, among other things, our indebtedness,

liens, fundamental changes, asset sales, investments and other matters. In addition, the Credit Agreement and the indenture governing the 2029 Notes each have a financial covenant requiring us to maintain liquidity of at least $25.0 million at all times. As a result, we are limited in the manner in which we conduct our business and we may be unable to engage in favorable business activities. The Credit Agreement and the indenture governing the 2029 Notes also contain certain events of default, after which the Term Loan or the 2029 Notes may be due and payable immediately, including, without limitation, withdrawal of approval for selinexor with respect to its current approved indication for use with bortezomib and dexamethasone, payment defaults, material inaccuracy of representations and warranties, covenant defaults, bankruptcy and insolvency proceedings, cross-defaults to certain other agreements, judgments against us and our subsidiaries, change in control and lien priority. Our obligations under the Credit Agreement and the indenture governing the 2029 Notes are secured by substantially all of our assets. Subject to the Intercreditor Agreement, in the event that an uncured default by us under the Credit Agreement or the indenture governing the 2029 Notes results in an acceleration of obligations thereunder, the Term Loan lenders and the holders of the 2029 Notes will have the right to foreclose on the collateral that was pledged to each such party. Any such foreclosure remedy would significantly and adversely affect us and could result in us losing our interest in such assets, which would have a material adverse impact on our business.

Our indebtedness could limit cash flow available for our operations, expose us to risks that could adversely affect our business, financial condition and results of operations and impair our ability to satisfy our obligations under the Term Loan, the 2029 Notes, the 2025 Notes or the Amended Revenue Interest Agreement.

We have incurred (i) $172.5 million of indebtedness as a result of the sale of the 2025 Notes, of which approximately $24.5 million remained outstanding following completion of the May 2024 exchange of certain of our 2025 Notes for 2029 Notes (the "Exchange Transactions"); (ii) $263.3 million of indebtedness under the Amended Revenue Interest Agreement, of which $135.0 million was repaid after giving effect to the May 2024 amendment to the Amended Revenue Interest Agreement, resulting in a remaining maximum aggregate repayment amount to HCRx of $128.3 million, (iii) $100.0 million of indebtedness under the Term Loan, and (iv) approximately $111.0 million of indebtedness as a result of the issuance of the 2029 Notes pursuant to the Exchange Transactions. We may also incur additional indebtedness to meet future financing needs, to the extent such indebtedness is available and permitted. Our indebtedness could have significant negative consequences for our security holders and our business, results of operations and financial condition by, among other things:

- increasing our vulnerability to adverse economic and industry conditions;
- limiting our ability to obtain additional financing;
- requiring the dedication of a substantial portion of our cash flow from operations to service our indebtedness, which would reduce the amount of cash available for other purposes;
- limiting our flexibility to plan for, or react to, changes in our business;
- diluting the interests of our existing stockholders as a result of issuing shares of our common stock upon conversion of the 2029 Notes or the 2025 Notes; and
- placing us at a possible competitive disadvantage with competitors that are less leveraged than we are or have better access to capital.

Our ability to pay the principal of or interest or other obligations on our present and any future indebtedness, including our remaining obligations to HCRx and under the Credit Agreement, the 2029 Notes and the 2025 Notes, or to make cash payments in connection with any conversion of the 2029 Notes or the 2025 Notes, depends on our future performance, which is subject, in part, to economic, financial, competitive and other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service the Term Loan, the Amended Revenue Interest Agreement, the 2029 Notes, the 2025 Notes or any other future indebtedness and make necessary capital expenditures.

We may not have the ability to raise the funds necessary to settle any conversions of or other obligations in respect of the 2029 Notes or the 2025 Notes required to be settled in cash, to repurchase the 2029 Notes or the 2025 Notes for cash upon a fundamental change, to pay the redemption price for any 2029 Notes or 2025 Notes we redeem or to refinance the 2029 Notes or the 2025 Notes, and any future debt we incur may contain limitations on our ability to pay cash upon conversion or repurchase of the 2029 Notes or the 2025 Notes.

Holders may require us to repurchase their 2029 Notes or 2025 Notes following a fundamental change at a cash repurchase price generally equal to the principal amount of the 2029 Notes or the 2025 Notes to be repurchased, plus accrued and unpaid interest. As discussed in more detail below under the risk factor entitled "*If we fail to maintain compliance with the continued listing requirements of Nasdaq, our common stock could be delisted from trading, which would adversely affect the liquidity of our common stock and our ability to raise additional capital. The transfer of our common stock to the Nasdaq Capital Market would result in a fundamental*

change under the indenture governing the 2025 Notes, which could negatively impact our financial condition", the transfer of the listing of our common stock to the Nasdaq Capital Market as a result of our failure to regain compliance with the Bid Price Rule by the Compliance Date (each as defined below) would constitute a fundamental change under the indenture governing the 2025 Notes, which could negatively impact our financial condition. In addition, with respect to the 2025 Notes, unless we elect to deliver solely shares of our common stock to settle conversions (other than paying cash in lieu of delivering any fractional share), we must satisfy any conversion in cash. If we do not have enough available cash at the time we are required to repurchase the 2029 Notes or the 2025 Notes, pay cash amounts due upon conversion or redemption of or otherwise required to be paid in respect of the 2029 Notes or the 2025 Notes or refinance the 2029 Notes or the 2025 Notes, we may be required to adopt one or more alternatives, such as selling assets, restructuring indebtedness or obtaining additional debt financing or equity capital on terms that may be onerous or highly dilutive. Our ability to refinance the 2029 Notes or the 2025 Notes or other future indebtedness will depend on the capital markets, our financial condition at such time and our obligations under any other existing indebtedness in effect at such time. We may not be able to engage in any of these activities on desirable terms, or at all, which could result in a default on our debt obligations, including the 2029 Notes and the 2025 Notes. In addition, our ability to repurchase the 2029 Notes or the 2025 Notes, to pay cash upon conversion or redemption of the 2029 Notes or the 2025 Notes or to refinance the 2029 Notes or the 2025 Notes may be limited by law, regulatory authority or agreements governing any future indebtedness that we may incur. Our failure to repurchase the 2029 Notes or the 2025 Notes at a time when the repurchase is required by the applicable indenture governing such notes or to pay cash upon conversion of or in respect of other obligations under the 2029 Notes or the 2025 Notes as required by the applicable indenture governing such notes would constitute a default under such indenture. A default under the indenture governing the 2029 Notes or the 2025 Notes or the fundamental change itself could also lead to a default under the Credit Agreement, the Amended Revenue Interest Agreement or agreements governing our future indebtedness, if any. Moreover, the occurrence of a fundamental change under the indenture governing the 2029 Notes or the 2025 Notes could constitute an event of default under any such agreements. If the repayment of the related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness and repurchase the 2029 Notes or the 2025 Notes or to pay cash upon conversion of the 2029 Notes or the 2025 Notes.

The conditional conversion feature of the 2025 Notes, if triggered, may adversely affect our financial condition and operating results.

In the event the conditional conversion feature of the 2025 Notes is triggered, holders of the 2025 Notes will be entitled to convert the 2025 Notes at any time during specified periods at their option. If one or more holders elects to convert their 2025 Notes, unless we elect to satisfy our conversion obligation by delivering solely shares of our common stock (other than paying cash in lieu of delivering any fractional share), we would be required to settle a portion or all of our conversion obligation in cash, which could adversely affect our liquidity. In addition, even if holders do not elect to convert their 2025 Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal amount of the 2025 Notes as a current rather than long-term liability, which would result in a material reduction of our net working capital.

The accounting method for convertible debt securities such as the 2025 Notes and the 2029 Notes could have a material effect on our reported financial results.

Conversions of the 2025 Notes may be settled in cash or shares, or a combination of cash and shares. Conversions of the 2029 Notes may only be settled in shares (subject to, and in accordance with, the settlement provisions of the indenture governing the 2029 Notes), plus cash in lieu of any fractional shares. Under the if-converted method, the maximum potential dilutive impact of the conversion of the 2025 Notes or the 2029 Notes is assumed when calculating diluted earnings per share during periods of net income. This could result in a material impact to diluted earnings per share. Diluted earnings per share is not impacted by the 2025 Notes or the 2029 Notes during periods of net loss.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our product candidates.

Until such time, if ever, as we can generate substantial revenues from the sale of our products, we expect to finance our cash needs through a combination of equity offerings, debt financings and refinancings, collaborations, strategic alliances and/or licensing arrangements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of common stockholders. In addition, our ability to raise additional capital through the sale of equity or convertible debt securities may be limited by the extent of our then remaining authorized and available shares of common stock. Debt financing, if available and permitted, 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. For example, during the terms of the Amended Revenue Interest Agreement, the Credit Agreement and the indenture governing the 2029 Notes, we cannot make any voluntary or optional cash payment or prepayment on our existing

convertible debt and cannot enter into any new debt without the consent of HCRx, the required lenders or the required holders, respectively, subject to the exceptions and other provisions under the applicable governing document.

If we raise additional funds through further collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our 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 research and drug development or current or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

Global credit and financial markets have experienced extreme disruptions over the past several years. Such disruptions have resulted, and could in the future result, in diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. Our general business strategy may be compromised by economic downturns, a volatile business environment and unpredictable and unstable market conditions, such as the current global situation resulting, in part, from the ongoing conflict between Russia and Ukraine, the war between Israel and Hamas, inflation, failures and instability in U.S. and international banking systems, sustained high interest rates and slower economic growth or recession. If the equity and credit markets deteriorate, it may make any necessary equity or debt financing more difficult to secure, more costly or more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could harm our growth strategy, financial performance and stock price and could require us to delay or abandon plans with respect to our business, including clinical development plans. Further, developments in the banking industry could adversely affect our business. If the financial institutions with which we do business enter receivership or become insolvent in the future, there is no guarantee that the Department of the Treasury, the Federal Reserve and the FDIC will intercede to provide us and other depositors with access to balances in excess of the $250,000 FDIC insurance limit, that we would be able to access our existing cash, cash equivalents and investments, that we would be able to maintain any required letters of credit or other credit support arrangements, or that we would be able to adequately fund our business for a prolonged period of time or at all, any of which could have a material adverse effect on our business, financial condition and results of operations. We cannot predict the impact that the high market volatility and instability of the banking sector more broadly could have on economic activity and our business in particular. In addition, there is a risk that one or more of our current service providers, manufacturers or other third parties with which we conduct business may not survive difficult economic times, including the current global situation resulting, in part, from the ongoing conflict between Russia and Ukraine, the war between Israel and Hamas, the instability of the banking sector, and the uncertainty associated with current worldwide economic conditions, which could directly affect our ability to attain our operating goals on schedule and on budget.

Risks Related to Our Dependence on Third Parties

We depend on collaborations with third parties for certain aspects of the development, marketing and/or commercialization of XPOVIO and/or our product candidates. If those collaborations are not successful, or if we are not able to maintain our existing collaborations or establish additional collaborations, we may have to alter our development and commercialization plans and may not be able to capitalize on the market potential of XPOVIO or our product candidates, if approved.

Our drug development programs and the commercialization of our products and product candidates, if approved, require local expertise and substantial additional cash to fund expenses. We expect to maintain our existing collaborations and collaborate with additional pharmaceutical and biotechnology companies for certain aspects of the development, marketing and/or commercialization of our products and product candidates. For example, we are party to license arrangements with Antengene and Menarini and distribution agreements with Promedico Ltd. and FORUS Therapeutics Inc. for the development, marketing and/or commercialization of selinexor in certain geographies outside of the U.S., and we expect to rely on additional partners to develop and commercialize our products outside of the U.S. In addition, we intend to seek one or more collaborators to aid in the further development, marketing and/or commercialization of selinexor and our other compounds for indications both within and outside of oncology. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K also apply to the activities, including activities in any country or territory outside of the U.S. and EU, as applicable, of our collaborators.

Potential collaborators include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies and we face significant competition in seeking appropriate collaborators, including as a result of a significant number of recent business combinations among large pharmaceutical companies that have reduced the number of potential collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon the assessment of the potential collaborator's expertise, its current and expected resources and competing priorities, 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 or foreign regulatory authorities, the potential market for the product or

product candidate, the costs and complexities of manufacturing and delivering such product or product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of intellectual property, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. A potential collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us.

Collaborations are complex and time consuming to negotiate, document and manage. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all, or we may be restricted under then-existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. If we are unable to maintain our current collaboration agreements or enter into new collaboration agreements, we may have to curtail, reduce or delay the development or commercialization programs for our products or product candidates, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms, or at all. If we do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements, and our collaboration agreements may not lead to the development or commercialization of our products or product candidates in the most efficient manner, or at all, and may result in lower product revenues or profitability to us than if we were to market and sell these products ourselves. In connection with any such arrangements with third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development, marketing and/or commercialization of our products or product candidates. Further, if our collaborations do not result in the successful development and commercialization of our products or product candidates or if any one of our collaborators terminates its agreement with us, we may not receive any future milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, the development and commercialization of our products or product candidates could be delayed and we may need additional resources to develop product candidates.

Collaborations involving our products and product candidates pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected or in compliance with applicable local and national laws and regulatory requirements;
- collaborators may not pursue development, marketing and/or commercialization of our products or product candidates or may elect not to continue or renew development, marketing or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus 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 may pursue a clinical and/or regulatory strategy for registration outside of the U.S. that would require our assistance and we may not have the resources to meet their or the regulators' timelines and/or expectations, which could delay or limit the development, commercialization or approval of our products outside the U.S.;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates 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 one or more products or product candidates may not commit sufficient resources to the marketing and distribution of our products or product candidates;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development or commercialization, might cause delays or termination of the research, development or commercialization of products or product candidates, might lead to additional responsibilities for us with respect to our products or product candidates, or might result in litigation or arbitration, any of which would be time consuming and expensive;

- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- we may lose certain valuable rights under circumstances identified in any collaboration arrangement that we enter into, such as if we undergo a change of control;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development, marketing and/or commercialization of the applicable products or product candidates or to enter into new collaboration agreements;
- collaborators may learn about our discoveries and use this knowledge to compete with us in the future; and
- the number and type of our collaborations could adversely affect our attractiveness to other collaborators or acquirers.

If any of these events occurs, the market potential of our products and product candidates, if approved, could be reduced, and our business could be materially harmed.

If we are unable to establish and maintain our agreements with third parties to distribute XPOVIO to patients, our results of operations and business could be adversely affected.

We rely on third parties to commercially distribute XPOVIO to patients. For example, we have contracted with a limited number of specialty pharmacies, which sell XPOVIO directly to patients, and specialty distributors, which sell XPOVIO to healthcare entities who then resell XPOVIO to patients. While we have entered into agreements with each of these pharmacies and distributors to distribute XPOVIO in the U.S., they may not perform as agreed or they may terminate their agreements with us. We may also need to enter into agreements with additional pharmacies or distributors, and there is no guarantee that we will be able to do so on a timely basis, at commercially reasonable terms, or at all. If we are unable to maintain and, if needed, expand, our network of specialty pharmacies and specialty distributors, we would be exposed to substantial distribution risk.

The use of specialty pharmacies and specialty distributors involves certain risks, including, but not limited to, risks that these organizations will:

- not provide us accurate or timely information regarding their inventories, the number of patients who are using XPOVIO or serious adverse reactions, events and/or product complaints regarding XPOVIO;
- not effectively sell or support XPOVIO or communicate publicly concerning XPOVIO in a manner that is contrary to FDA rules and regulations;
- reduce their efforts or discontinue to sell or support, or otherwise not effectively sell or support, XPOVIO;
- not devote the resources necessary to sell XPOVIO in the volumes and within the timeframes that we expect;
- be unable to satisfy financial obligations to us or others; or
- cease operations.

Any such events may result in decreased product sales, which would harm our results of operations and business.

We rely on third parties as we conduct our clinical trials and some aspects of our research and preclinical studies, and those third parties may not perform satisfactorily, including not meeting local regulatory submission requirements or failing to meet deadlines for the completion of such trials, research or testing.

We rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, as we conduct our clinical trials. We currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical studies. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our drug development activities.

Our reliance on these third parties for research and development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with GCP

standards when conducting, recording and reporting the results of clinical trials to ensure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. The EMA also requires us to comply with comparable standards. Regulatory authorities ensure compliance with these requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of the third parties that we rely on in connection with our clinical trials fail to comply with applicable requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or other 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 such requirements. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, such as clinicaltrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our products. In such an event, our financial results and the commercial prospects for our products or product candidates, if approved, could be harmed, our costs could increase and our ability to generate revenues could be delayed, impaired or foreclosed.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of such third parties could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We rely on third parties to conduct investigator-sponsored clinical trials of selinexor and our other product candidates. Any failure by a third party to meet its obligations with respect to the clinical development of our product candidates may delay or impair our ability to obtain regulatory approval for selinexor and our other product candidates.

We rely on academic and private non-academic institutions to conduct and sponsor clinical trials relating to selinexor and our other product candidates, such as the European Myeloma Network, which is the sponsor of our ongoing randomized global Phase 3 trial evaluating selinexor in combination with pomalidomide and dexamethasone versus elotuzumab, pomalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. We do not solely control the design or conduct of the investigator-sponsored trials, and it is possible that the FDA or foreign regulatory authorities will not view these investigator-sponsored trials as providing adequate support for future clinical trials, whether controlled by us or third parties, for any one or more reasons, including elements of the design, execution of the trials, safety concerns or other trial results.

Such arrangements will provide us certain information rights with respect to the investigator-sponsored trials, such as access to and the ability to use and reference the data, including for our own regulatory filings, resulting from the investigator-sponsored trials. However, we do not have control over the timing and reporting of the data from investigator-sponsored trials, nor do we own the data from the investigator-sponsored trials. If we are unable to confirm or replicate the results from the investigator-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing clinical development of our product candidates. Further, if investigators or institutions breach their obligations with respect to the clinical development of our product candidates, or if the data proves to be inadequate compared to the first-hand knowledge we might have gained had the investigator-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

Additionally, the FDA or foreign regulatory authorities may disagree with the sufficiency of our right to reference the preclinical, manufacturing or clinical data generated by these investigator-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these investigator-sponsored trials. If so, the FDA or foreign regulatory authorities may require us to obtain and submit additional preclinical, manufacturing, or clinical data before we may initiate our planned trials and/or may not accept such additional data as adequate to initiate our planned trials.

We are completely dependent on third parties for the manufacture of our products and product candidates and any difficulties, disruptions, delays or unexpected costs, or the need to find alternative sources, could adversely affect our results of operations, profitability and future business prospects.

We do not own or operate, and currently have no plans to establish, any manufacturing facilities for our products or product candidates. We currently rely, and expect to continue to rely, on third-party contract manufacturers to manufacture our products and product candidates for our commercial and clinical use.

Facilities used by our third-party manufacturers may be inspected by the FDA after we submit a marketing application and before potential approval of the product candidate and are also subject to ongoing periodic unannounced inspections by the FDA for compliance with cGMP and other regulatory requirements following approval. Similar regulations apply to manufacturers of our product candidates for use or sale in foreign countries. We do not control the manufacturing processes of, and are completely dependent on, our third-party manufacturers for compliance with the applicable regulatory requirements for the manufacture of our products and product candidates. Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the U.S. If our manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA and any applicable foreign regulatory authority, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. If these facilities are not approved for commercial manufacture or are not able to maintain approval, we may need to find alternative manufacturing facilities, which could significantly impact our ability to develop, obtain regulatory approval for or market our products or product candidates as alternative qualified manufacturing facilities may not be available on a timely or cost-efficient basis, or at all. Failure by any of our manufacturers to comply with applicable cGMP regulations or other regulatory requirements could result in sanctions being imposed on us or the contract manufacturer, including fines, injunctions, civil penalties, delays, suspensions or withdrawals of approvals, operating restrictions, interruptions in supply and criminal prosecutions, any of which could significantly and adversely affect supplies of our products or product candidates and have a material adverse impact on our business, financial condition and results of operations.

The clinical and commercial supplies of the drug product for XPOVIO are currently manufactured pursuant to a combination of long-term supply agreements and as-needed purchase order agreements with our third-party manufacturers. Our ability to have our products manufactured in sufficient quantities and at acceptable costs to meet our commercial demand and clinical development needs is dependent on the uninterrupted and efficient operation of our third-party contract manufacturers' facilities. Further, through our third-party contract manufacturers and data service providers, we provide serialized commercial products as required to comply with the DSCSA and its foreign equivalents where applicable. If our third-party contract manufacturers or data service providers fail to support our efforts to continue to serialize, track, trace and authenticate units of our products in compliance with these requirements and their and their foreign equivalents, as well as any future requirements, we may face legal penalties or be restricted from selling our products.

Reliance on third-party manufacturers entails other risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach, termination or nonrenewal of a manufacturing agreement by the third party, including at a time that is costly or inconvenient to us;
- the possible failure of the third party to manufacture our products or product candidates according to our schedule, or at all, including if the third-party manufacturer gives greater priority to the supply of other products over our products and product candidates, or otherwise does not satisfactorily perform according to the terms of the manufacturing agreement;
- equipment malfunctions, power outages or other general disruptions experienced by our third-party manufacturers to their respective operations and other general problems with a multi-step manufacturing process; and
- the possible misappropriation or disclosure by the third party or others of our proprietary information, including our trade secrets and know-how.

We currently rely on a single source supplier for our active pharmaceutical ingredient and our drug product manufacturing requirements. Any performance failure on the part of our existing or future manufacturers could delay clinical development, marketing approval or commercialization of our products or product candidates. If our suppliers or contract manufacturers are so affected, our supply chain could be disrupted, our product shipments could be delayed, our costs could be increased and our business could be adversely affected. If our current contract manufacturers cannot perform as agreed, we may be required to replace those manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our products and product candidates, we could incur added costs and delays in identifying and qualifying any such replacement. Consequently, we may not be able to reach agreement with third-party manufacturers on satisfactory terms, which could negatively impact our XPOVIO revenues or delay commercialization of any product candidates that are subsequently approved.

If, because of the factors discussed above, we are unable to have our products manufactured on a timely or sufficient basis, we may not be able to meet clinical development needs or commercial demand for our products or product candidates or we may not be able to manufacture our products in a cost-effective manner. As a result, we may lose sales, fail to generate projected revenues or suffer development or regulatory setbacks, any of which could have an adverse impact on our profitability and future business prospects.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our products or product candidates and other discoveries, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize drugs and other discoveries similar or identical to ours, and our ability to successfully commercialize our products or product candidates and other discoveries may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the U.S. and other countries with respect to our proprietary products and product candidates and other discoveries. We seek to protect our proprietary position by filing patent applications related to our novel products and product candidates and other discoveries that are important to our business. As of February 14, 2025, 182 patents were in force that relate to exportin 1 inhibitors, including composition of matter patents for selinexor, verdinexor and eltanexor in the U.S., and their use in targeted therapeutics. In addition, 32 patents were in force that relate to our PAK4/NAMPT inhibitors, including three composition of matter patents for KPT-9274 in the U.S. and its use in targeted therapeutics. With respect to our KPT-1200 program, as of February 14, 2025, 12 patents were in force that relate to IL-12 compositions and uses of IL-12 in targeted therapeutics. We cannot be certain that any other patents will issue with claims that cover any of our key products, product candidates or other discoveries.

The patent prosecution process is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. 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.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. 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 our product candidates or other discoveries, or which effectively prevent others from commercializing competitive drugs and discoveries. Changes in either the patent laws or interpretation of the patent laws in the U.S. and other countries may diminish the value of our patents or narrow the scope of our patent protection.

The laws of foreign countries may not protect our rights to the same extent as the laws of the U.S. For example, in some foreign jurisdictions, our ability to secure patents based on our filings in the U.S. may depend, in part, on our ability to timely obtain assignment of rights to the invention from the employees and consultants who invented the technology. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the U.S. 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 patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

Assuming the other requirements for patentability are met, prior to March 2013, in the U.S., the first to invent the claimed invention was entitled to the patent, while outside of the U.S., the first to file a patent application is entitled to the patent. In March 2013, the U.S. transitioned to a first-inventor-to-file system in which, assuming the other requirements for patentability are met, the first inventor to file a patent application is entitled to the patent. We may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office ("USPTO") or become involved in opposition, derivation, revocation, reexamination, or post-grant or inter partes review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our discoveries or drugs and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative discoveries or drugs in a non-infringing manner.

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 U.S. and abroad. Such challenges may result in 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 discoveries and drugs, or limit the duration of the patent protection of our products, product candidates and discoveries. 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 drugs similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time consuming and unsuccessful.

Competitors or commercial supply companies or others may infringe our patents and other intellectual property rights. For example, we are aware of third parties selling a version of our lead product candidate for research purposes, which may infringe our intellectual property rights. To counter such infringement, we may advise such companies of our intellectual property rights, including, in some cases, intellectual property rights that provide protection for our lead product candidates, and demand that they stop infringing those rights. Such demand may provide such companies the opportunity to challenge the validity of certain of our intellectual property rights, or the opportunity to seek a finding that their activities do not infringe our intellectual property rights. We may also be required to file infringement actions, which can be expensive and time consuming. In an infringement proceeding, a defendant may assert and a court may agree with a defendant that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the intellectual property at issue. An adverse result in any litigation could put one or more of our patents at risk of being invalidated or interpreted narrowly. 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 during this type of litigation.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of any current and future collaborators to develop, manufacture, market and sell XPOVIO and our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products or product candidates and technology, including interference proceedings before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. No litigation asserting such infringement claims is currently pending against us, and we have not been found by a court of competent jurisdiction to have infringed a third party's intellectual property rights. If we are found to infringe or think there is a risk we may be found to infringe, a third party's intellectual property rights, we could be required or choose to obtain a license from such third party to continue developing, marketing and selling our products, product candidates and technology. However, we may not be able to obtain any required license on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same intellectual property licensed to us. We could be forced, including by court order, to cease commercializing the infringing intellectual property or product or to cease using the infringing technology. In addition, we could be found liable for monetary damages. A finding of infringement could prevent us from commercializing our products or product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Although we have no knowledge of any such claims being alleged to date, if such claims were to arise, litigation may be necessary to defend against any such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock. 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 adequately conduct such litigation or proceedings. Some of 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 have a material adverse effect on our ability to compete in the marketplace.

Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment and other requirements imposed by 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 the patents and/or applications. We have systems in place to remind us to pay these fees, and we rely on our outside counsel 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 with such provisions, 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 non-compliance 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, it could have a material adverse effect on our business.

If our product candidates or any of our future product candidates obtain regulatory approval, additional competitors could enter the market with generic versions of such products, which may result in a material decline in sales of our competing products.

Under the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments") to the FDCA, a company may file an ANDA, seeking approval of a generic version of an approved innovator product. Under the Hatch-Waxman Amendments, a company may also submit an NDA under section 505(b)(2) of the FDCA that references the FDA's prior approval of the innovator product or preclinical studies and/or clinical trials that were not conducted by, or for, the sponsor and for which the sponsor has not obtained a right of reference. A 505(b)(2) NDA product may be for a new or improved version of the original innovator product. The Hatch-Waxman Amendments also provide for certain periods of regulatory exclusivity, which preclude FDA approval (or in some circumstances, FDA filing and review) of an ANDA or 505(b)(2) NDA.

In certain circumstances, third parties may file an ANDA or NDA under Section 505(b)(2) as early as the so-called "NCE-1" date that is one year before the expiry of the five-year period of New Chemical Entity exclusivity or more generally four years after NDA approval. The third parties are allowed to rely on the safety and effectiveness data of the innovator's product, may not need to conduct clinical trials and can market a competing version of a product after the expiration or loss of patent exclusivity or the expiration or loss of regulatory exclusivity and often charge significantly lower prices. Upon the expiration or loss of patent protection or the expiration or loss of regulatory exclusivity for a product, the major portion of revenues for that product may be dramatically reduced in a very short period of time. If we are not successful in defending our patents and regulatory exclusivities, we will not derive the expected benefit from them. For example, the NCE-1 date for selinexor was July 3, 2023 after which a third party could be positioned to market an ANDA or Section 505(b)(2) product that competes with selinexor prior to the expiry of our patents if the third party successfully challenged the validity of our patents protecting the product.

In addition to the benefits of regulatory exclusivity, an innovator NDA holder may have patents claiming the active ingredient, product formulation or an approved use of the drug, which would be listed with the product in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the Orange Book. If there are patents listed in the Orange Book for the applicable, approved innovator product, a generic or 505(b)(2) sponsor that seeks to market its product before expiration of the patents must include in their applications what is known as a "Paragraph IV" certification, challenging the validity or enforceability, or claiming non-infringement, of the listed patent or patents. Notice of the certification must be given to the patent owner and NDA holder and if, within 45 days of receiving notice, either the patent owner or NDA holder sues for patent infringement, approval of the ANDA or 505(b)(2) NDA is stayed for up to 30 months.

Accordingly, if any of our product candidates that are regulated as drugs are approved, competitors could file ANDAs for generic versions of these products or 505(b)(2) NDAs that reference our products. If there are patents listed for such drug products in the Orange Book, those ANDAs and 505(b)(2) NDAs would be required to include a certification as to each listed patent indicating whether the ANDA sponsor does or does not intend to challenge the patent. We cannot predict which, if any, patents in our current portfolio or patents we may obtain in the future will be eligible for listing in the Orange Book, how any generic competitor would address such patents, whether we would sue on any such patents or the outcome of any such suit.

If we do not successfully extend the term of patents covering our product candidates under the Hatch-Waxman Amendments and similar foreign legislation, our business may be materially harmed.

Depending upon the timing, duration and conditions of FDA marketing approval, if any, of our products or product candidates, one or more of our U.S. patents may be eligible for patent term extension under the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent term extension of up to five years for one patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. However, we may not receive an extension if we 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. The total patent term, including the extension period, may not exceed 14 years following FDA approval. Accordingly, the length of the extension, or the ability to even obtain an extension, depends on many factors.

In the U.S., only a single patent can be extended for each qualifying FDA approval, and any patent can be extended only once and only for a single product. Laws governing analogous patent term extensions in foreign jurisdictions vary widely, as do laws governing the ability to obtain multiple patents from a single patent family. Because both selinexor and verdinexor are protected by a single family of patents and applications, we may not be able to secure patent term extensions for both of these product candidates in all jurisdictions where these product candidates are approved.

If we are unable to obtain a patent term extension for a product or product candidate or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that product or product candidate, if any, in that jurisdiction will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue could be materially reduced.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for our products, product candidates and other discoveries, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. 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. To the extent that we are unable to timely enter into confidentiality and invention or patent assignment agreements with our employees and consultants, our ability to protect our business through trade secrets and patents may be harmed. 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 of the U.S. are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed. To the extent inventions are made by a third party under an agreement that does not grant us an assignment of their rights in inventions, we may choose or be required to obtain a license.

Not all of our trademarks are registered. Failure to secure those registrations could adversely affect our business.

As of February 14, 2025, we have trademark registrations in the U.S. for KARYOPHARM, KARYOPHARM THERAPEUTICS, our color logo, our logo in grayscale, KARYOPHARM THERAPEUTICS with the color logo, XPOVIO, PORE for our online research portal, and KARYFORWARD and our KARYFORWARD logo for our financial aid and charitable services. Outside of the U.S., XPOVIO is registered or pending in 46 additional jurisdictions, and is registered in Katakana in Japan, Hangul in South Korea, and Chinese characters in Taiwan. KARYOPHARM, the greyscale logo, KARYOPHARM THERAPEUTICS with the color logo, and the KARYFORWARD logo are each registered in four jurisdictions outside of the U.S. We also have registrations or applications for eight additional possible drug names in numerous foreign jurisdictions. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would, which could adversely affect our business. During trademark registration proceedings in the U.S. and foreign jurisdictions, we may receive rejections. We are given an opportunity to respond to those rejections, but we may not be able to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings.

In addition, any proprietary name we propose to use with our key product candidates in the U.S. must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed

drug names, including an evaluation of potential for confusion with other drug names. If the FDA objects to any of our proposed proprietary drug names for any of our product candidates, if approved, we may be required to expend significant additional resources in an effort to identify a suitable proprietary drug name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

Risks Related to Our Operations and Employee Matters

Our future success depends on our ability to retain key members of our management team and to attract, retain and motivate qualified personnel.

We are highly dependent on the management, technical and scientific expertise of principal members of our management and scientific teams, including our President and Chief Executive Officer. Although we have entered into formal employment agreements with our executive officers, these agreements do not prevent them from terminating their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees. The loss of the services of any of our key employees could impede the achievement of our research, development, commercialization and other business objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel is critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategies. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

Our business and operations may be materially adversely affected in the event of information technology system failures or security breaches, and the costs and consequences of implementing data protection measures could be significant.

Despite the implementation of security measures, our internal computer systems, and those of our CROs and other third parties on which we rely, are vulnerable to damage or other impacts from cyber-attacks, computer viruses, unauthorized access, sabotage, natural disasters, fire, terrorism, war and telecommunication and electrical failures. Such systems are also vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors and/or business partners, or from cyber incidents initiated by malicious third parties. Cyber incidents continue to increase in their frequency, sophistication and intensity, and have become increasingly difficult to detect, respond to and recover from. Cyber incidents could include the deployment of harmful malware, ransomware, denial-of-service attacks, unauthorized access to or deletion of files, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber incidents also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal data of our employees. In addition, outside parties may attempt to penetrate our systems or those of our vendors or fraudulently induce our employees or employees of our vendors to disclose sensitive information to gain access to our data. Like other companies, we may experience threats to our data and systems, including malicious codes and viruses, and other cyber-attacks. In addition, we face other kinds of risks related to our commercial and personal data, including lost or stolen devices or other systems (including paper records) that collect and store our personal and commercial information. Furthermore, our manufacturing vendors could also be subject to a cyber-attack that could negatively impact the manufacturing process of our products and/or product candidates, which could, in turn, harm our patients, result in a product recall, or provide uncertain medical or trial results.

We are aware of certain vendors who have been impacted by cyber-attacks, inclusive of but not limited to ransomware, phishing, and spam. While such events have not directly impacted us, similar events in the future could have a material impact on us. If a cyber-attack or other security incident were to occur and cause interruptions in our operations, it could result in a material disruption of our development and commercialization programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our reputation or competitive position could be damaged, and the further development and commercialization of our products or product candidates could be delayed or halted. We may not have adequate insurance coverage to provide compensation for any losses associated with such events. In addition, we may in certain instances be required to provide notification to individuals or others in connection with the loss of their personal or commercial information.

Additionally, global tensions continue to raise the possibility of nation state attacks on critical infrastructure like power, telecommunications, and water in the U.S. and around the world. Attacks on telecommunications infrastructure in particular could impact our business operations globally, and would likely be outside our ability to detect or respond to, beyond noting that telecommunications services had been impacted.

If a material breach of our security or that of our vendors occurs, our financial or other confidential information could be compromised, the market perception of the effectiveness of our security measures could be harmed, we could lose business, our reputation and credibility could be damaged and we could be subject to legal proceedings. In addition, the cost and operational consequences of implementing further data protection measures could be significant. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. The development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely.

Risks Related to Our Common Stock

If we fail to maintain compliance with the continued listing requirements of Nasdaq, our common stock could be delisted from trading, which would adversely affect the liquidity of our common stock and our ability to raise additional capital. The transfer of our common stock to the Nasdaq Capital Market would result in a fundamental change under the indenture governing the 2025 Notes, which could negatively impact our financial condition.

On September 16, 2024, we received a deficiency letter from the Listing Qualifications Department (the "Staff") of the Nasdaq Stock Market ("Nasdaq") notifying us that, for the last 32 consecutive business days, the bid price of our common stock had closed below the minimum $1.00 per share requirement for continued inclusion on the Nasdaq Global Select Market pursuant to Nasdaq Listing Rule 5450(a)(1) (the "Bid Price Rule"). The deficiency letter does not result in the immediate delisting of our common stock from the Nasdaq Global Select Market. In accordance with Nasdaq Listing Rule 5810(c)(3)(A), we have been provided an initial period of 180 calendar days, or until March 17, 2025 (the "Compliance Date"), to regain compliance with the Bid Price Rule. If, at any time before the Compliance Date, the bid price for our common stock closes at $1.00 per share or more for a minimum of 10 consecutive business days, as required by the Compliance Period Rule, the Staff will provide written notification to us that we comply with the Bid Price Rule, unless the Staff exercises its discretion to extend this 10-day period pursuant to Nasdaq Listing Rule 5810(c)(3)(H).

If we do not regain compliance with the Bid Price Rule by the Compliance Date, we may be eligible for an additional 180 calendar day compliance period. To qualify, we would be required to transfer the listing of our common stock to the Nasdaq Capital Market, provided that we meet the continued listing requirements for the market value of publicly held shares and all other initial listing standards of the Nasdaq Capital Market, with the exception of its bid requirement. To effect such a transfer, among other things, we would also need to pay an application fee to Nasdaq and provide written notice to the Staff of our intention to cure the deficiency during the additional compliance period by effecting a reverse stock split, if necessary. However, as discussed above under the risk factor entitled "We may not have the ability to raise the funds necessary to settle any conversions of or other obligations in respect of the 2029 Notes or the 2025 Notes required to be settled in cash, to repurchase the 2029 Notes or the 2025 Notes for cash upon a fundamental change, to pay the redemption price for any 2029 Notes or 2025 Notes we redeem or to refinance the 2029 Notes or the 2025 Notes, and any future debt we incur may contain limitations on our ability to pay cash upon conversion or repurchase of the 2029 Notes or the 2025 Notes", the indenture governing the 2025 Notes treats a transfer of listing to the Nasdaq Capital Market as a "fundamental change" that gives the holders of the 2025 Convertible Notes a right to require us to repurchase the 2025 Convertible Notes for cash, which may severely limit our ability to effect such a transfer and utilize the additional 180 day compliance period.

If we do not regain compliance with the Bid Price Rule by the Compliance Date and it appears to the Staff that we will not be able to regain compliance with the Bid Price Rule during the additional compliance period, or that due to limitations in the indenture governing the 2025 Notes or for other reasons, we are otherwise not eligible for an additional compliance period at that time, the Staff will provide written notification to us that our common stock will be subject to delisting. At that time, we may appeal the Staff's delisting determination to a Nasdaq Listing Qualifications Panel (the "Panel"). We expect that our common stock would remain listed pending the Panel's decision. However, there can be no assurance that, if we do appeal the delisting determination by the Staff to the Panel, that such appeal would be successful.

We intend to monitor the closing bid price of our common stock and may, if appropriate, consider available options to regain compliance with the Bid Price Rule, which could include seeking to effect a reverse stock split. On January 30, 2025, our stockholders approved, among other things, an amendment to our Restated Certificate of Incorporation to effect a reverse stock split of our issued shares of common stock at a ratio within the range of not less than 1-for-5 and not greater than 1-for-15, and a proportionate reduction in the number of authorized shares of common stock, with the exact ratio within such range and the implementation and timing of

such reverse stock split to be determined at the sole discretion of our Board of Directors, without further approval or authorization of our stockholders. However, there can be no assurances that we will be able to regain compliance with the Bid Price Rule.

There are many factors that may adversely affect our minimum bid price, including those described throughout this "Risk Factors" section. Many of these factors are outside of our control. As a result, we may not be able to sustain compliance with the Bid Price Rule in the long term. Any potential delisting of our common stock from the Nasdaq Global Select Market would likely result in decreased liquidity and increased volatility for our common stock and would adversely affect our ability to raise additional capital or to enter into strategic transactions. Any potential delisting of our common stock from the Nasdaq Global Select Market would make it more difficult for our stockholders to sell our common stock in the public market. Further, the transfer of the listing of our common stock to another nationally recognized stock exchange other than the New York Stock Exchange, Nasdaq Global Select Market or Nasdaq Global Market could also negatively impact our financial condition as it would constitute a fundamental change under the indenture governing the 2025 Notes, giving the holders thereof the right to require us to repurchase the Notes for cash. For additional risks associated with a fundamental change under the indenture governing the 2025 Notes, please see the risk factor entitled "We may not have the ability to raise the funds necessary to settle any conversions of or other obligations in respect of the 2029 Notes or the 2025 Notes required to be settled in cash, to repurchase the 2029 Notes or the 2025 Notes for cash upon a fundamental change, to pay the redemption price for any 2029 Notes or 2025 Notes we redeem or to refinance the 2029 Notes or the 2025 Notes, and any future debt we incur may contain limitations on our ability to pay cash upon conversion or repurchase of the 2029 Notes or the 2025 Notes".

Provisions in our corporate charter documents and under 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.

Provisions in our corporate charter and our 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 stockholders might otherwise receive a premium for their shares. These provisions could also 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;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "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 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% 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 in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

The price of our common stock has been and may continue to be volatile and your investment in our stock could decline in value or fluctuate significantly, including as a result of analysts' activities.

Our stock price has been, and may continue to be, volatile and your investment in our stock could decline or fluctuate significantly. Our common stock price has ranged from $0.59 to $1.58 in the 52-week period ended February 14, 2025. On February 14, 2025, the closing sale price of our common stock on the Nasdaq Global Select Market was $0.62 per share. The stock market in general and the market for pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has

often been unrelated to the operating performance of particular companies, such as the response to world-wide economic disruptions related to the COVID-19 pandemic, the conflict between Russia and Ukraine, the war between Israel and Hamas, inflation and sustained high interest rates. The market price for our common stock may be influenced by many factors, including:

- our failure or perceived failure to successfully execute on our commercialization strategy for XPOVIO or our product candidates, if approved;
- the level of success of competitive products or technologies;
- results, delays in, or the halting of our clinical trials or those of our competitors, including reports of AEs related to the use of our products;
- announcements by us or our competitors of new products or data, significant mergers, acquisitions, licenses or joint ventures;
- commencement or termination of collaborations for our development programs and the commercialization of our products;
- adverse regulatory or legal developments in the U.S. and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- additions or departures of key personnel;
- the level of expenses related to the commercialization of XPOVIO and clinical development programs for any of our product candidates;
- the results of our efforts to discover, develop, acquire or in-license additional products or product candidates;
- actual or anticipated changes in estimates of financial results or guidance, clinical development timelines or recommendations by securities analysts;
- actual or anticipated fluctuations in our quarterly or annual financial results;
- changes in healthcare laws affecting pricing, reimbursement or access;
- market conditions in the pharmaceutical and biotechnology sectors, including as the result of uncertainties due to or impacts from pandemics or other public health emergencies;
- general economic, industry and market conditions, such as those caused by the ongoing conflict between Russia and Ukraine, the war between Israel and Hamas, inflation and fluctuations in interest rates;
- our ability to raise additional capital and/or refinance our debt and the terms on which we can raise capital and/or refinance debt;
- sales of large blocks of our common stock, including by our executive officers, directors and significant stockholders, or substantial changes in short interest in our common stock; and
- the other risks and uncertainties described in this "*Risk Factors*" section.

The COVID-19 pandemic caused significant disruptions in the financial markets and also impacted the volatility of our stock price and trading in our stock. In addition, U.S. and global markets are experiencing volatility and disruption following the escalation of geopolitical tensions and the ongoing conflict between Russia and Ukraine, the war between Israel and Hamas, inflation and sustained high interest rates. A continuation or worsening of the levels of market disruption and volatility could have an adverse effect on the market price of our common stock. Furthermore, the trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. Our stock price could decline significantly if we fail to meet or exceed analysts' forecasts and expectations or if one or more of the analysts covering our business downgrade their evaluations of our stock. Further, if one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

Securities or other litigation could result in substantial costs and may divert management's time and attention from our business.

Securities class action litigation is often brought against a company following a decline or periods of volatility in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years, including as a result of the COVID-19 pandemic, and we are therefore a target of this type of litigation. For example, we were subject to a class action lawsuit and a shareholder derivative lawsuit alleging federal securities laws violations,

both of which have been dismissed. We may face additional securities class action litigation or other litigation in the future, including if we fail to successfully commercialize XPOVIO, or if we cannot obtain regulatory approvals for, or if we otherwise fail to successfully commercialize and launch, our product candidates.

The outcome of litigation is necessarily uncertain, and we could be forced to expend significant resources in the defense of such suits, and we may not prevail. Monitoring and defending against legal actions is time consuming for our management and detracts from our ability to fully focus our internal resources on our business activities. In addition, we may incur substantial legal fees and costs in connection with any such litigation. We have not established any reserves for any potential liability relating to any such potential lawsuits. It is possible that we could, in the future, incur judgments or enter into settlements of claims for monetary damages. We currently maintain insurance coverage for some of these potential liabilities. Other potential liabilities may not be covered by insurance, insurers may dispute coverage or the amount of insurance may not be enough to cover damages awarded. In addition, certain types of damages may not be covered by insurance, and insurance coverage for all or certain forms of liability may become unavailable or prohibitively expensive in the future. A decision adverse to our interests on one or more legal matters or litigation could result in the payment of substantial damages, or possibly fines, and could have a material adverse effect on our reputation, financial condition and results of operations.

We have broad discretion in the use of our cash, cash equivalents and investments and may not use them effectively.

Our management has broad discretion to use our cash, cash equivalents and investments to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use to fund our operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

We are a "smaller reporting company", and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

We are a "smaller reporting company," as defined in Rule 12b-2 under the Securities Exchange Act of 1934, as amended. We would cease to be a smaller reporting company if (i) we have a public float of $250 million or more and have annual revenues in excess of $100 million or (ii) if we have a public float of $700 million or more, determined on an annual basis.

As a smaller reporting company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not smaller reporting companies. These exemptions include:

- reduced disclosure obligations regarding executive compensation;
- being permitted to provide only two years of audited financial statements in our annual report on Form 10-K, with corresponding reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure; and
- not being required to furnish a stock performance graph in our annual report.

We cannot predict whether investors will find our common stock less attractive as a result of any reliance by us on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

If we identify a material weakness in our internal control over financial reporting, it could have an adverse effect on our business and financial results and our ability to meet our reporting obligations could be negatively affected, each of which could negatively affect the trading price of our common stock.

A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. Accordingly, a material weakness increases the risk that the financial information we report contains material errors.

We regularly review and update our internal controls, disclosure controls and procedures, and corporate governance policies. In addition, we are required under the Sarbanes-Oxley Act of 2002 to report annually on our internal control over financial reporting. Any system of internal controls, however well designed and operated, is based in part on certain assumptions and can provide only reasonable, not absolute, assurances that the objectives of the system are met. If we, or our independent registered public accounting firm, determine that our internal control over our financial reporting is not effective, or we discover areas that need improvement in

the future, or we experience high turnover of our personnel in our financial reporting functions, these shortcomings could have an adverse effect on our business and financial results, and the price of our common stock could be negatively affected.

If we cannot conclude that we have effective internal control over our financial reporting, or if our independent registered public accounting firm is unable to provide an unqualified opinion regarding the effectiveness of our internal control over financial reporting, investors could lose confidence in the reliability of our financial statements, which could lead to a decline in our stock price. Failure to comply with reporting requirements could also subject us to sanctions and/or investigations by the SEC, the Nasdaq Stock Market or other regulatory authorities.

If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements, our projected guidance and/or our projected market opportunities prove inaccurate, our actual results may vary from those reflected in our projections and accruals.

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP"). The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges accrued by us and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances.

We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct. Further, from time to time we issue guidance on our expected financial performance for future periods, such as our expectations regarding our revenue, non-GAAP research and development and selling, general and administrative expenses, and cash, cash equivalents and investments available for operations, which guidance is based on estimates and the judgment of management. If, for any reason, our actual results differ materially from our guidance, we may have to adjust our publicly announced financial guidance. If we fail to meet, or if we are required to change or update any element of, our publicly disclosed financial guidance or other expectations about our business, our stock price could decline.

Further our estimates of the potential market opportunities for XPOVIO and our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions has not been assessed by an independent source. If any of our assumptions or estimates, or these publications, research, surveys or studies prove to be inaccurate, then the actual market for XPOVIO or any other products or product candidates may be smaller than we expect, and as a result our product revenue may be limited and it may be more difficult for us to achieve profitability.

Our ability to use our net operating loss carryforwards and tax credit carryforwards to offset future taxable income may be subject to certain limitations.

Under the provisions of the Internal Revenue Code of 1986, as amended (the "Code"), our net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service (and state tax authorities under relevant state tax rules). In addition, as described below in "Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition," the TCJA, as amended by the Coronavirus Aid, Relief and Economic Security Act (the "CARES Act"), includes changes to U.S. federal tax rates and the rules governing net operating loss carryforwards that may significantly impact our ability to utilize our net operating losses to offset taxable income in the future. Furthermore, the use of net operating loss and tax credit carryforwards may become subject to an annual limitation under Sections 382 and 383 of the Code, respectively, and similar state provisions in the event of certain cumulative changes in the ownership interest of significant stockholders in excess of 50 percent over a three-year period. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of a company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. Our company has completed several financings since its inception which resulted in an ownership change under Sections 382 and 383 of the Code. In addition, future changes in our stock ownership, some of which are outside of our control, could result in ownership changes in the future. For these reasons, we may not be able to use some or all of our net operating loss and tax credit carryforwards, even if we attain profitability.

Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

Changes in tax law may adversely affect our business or financial condition. For example, the TCJA, as amended by the CARES Act, significantly revised the Code. The TCJA, as amended by the CARES Act, among other things, contained significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21% and, for taxable years beginning after December 31, 2020, limitation of the deduction for net operating losses to 80% of current year taxable income for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely). In addition, beginning in 2022, the TCJA eliminated the option to deduct research and development expenditures currently and requires corporations to capitalize and amortize them over five years or 15 years for expenditures attributable to foreign research.

In addition to the CARES Act, as part of Congress' response to the COVID-19 pandemic, economic relief legislation was enacted in 2020 and 2021 containing tax provisions. Further, as of August 2022, the IRA introduced new tax provisions, including a one percent excise tax imposed on certain stock repurchases by publicly traded companies. The one percent excise tax generally applies to any acquisition of stock by the publicly traded company (or certain of its affiliates) from a stockholder of the company in exchange for money or other property (other than stock of the company itself), subject to a de minimis exception. Thus, the excise tax could apply to certain transactions that are not traditional stock repurchases. Regulatory guidance under the TCJA and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen their impact on our business and financial condition. In addition, it is uncertain if and to what extent various states will conform to the TCJA and additional tax legislation.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 1C. Cybersecurity

Cybersecurity Risk Management and Strategy

As is the case for most companies, we are regularly subject to cyberattacks and other cyber incidents, and, therefore, cybersecurity is an important element of our ongoing information technology operations. We devote significant resources to protecting and enhancing the security of our computer systems, business information, software, networks and other technology assets, by applying our cybersecurity risk management processes, which consider physical, procedural and technical safeguards. We have a multi-faceted program for assessing, identifying and managing cybersecurity risks, that is designed to help protect our information assets and operations from internal and external cyber threats by:

- organizing our cybersecurity efforts based on the National Institute of Standards and Technology ("NIST") Cybersecurity Framework by applying the framework's rubric of Govern, Identify, Protect, Detect, Respond, and Recover;
- seeking to understand, manage and mitigate risk while ensuring business resiliency and protecting business, employee and patient information from unauthorized access or attack;
- identifying critical business information, the lifecycles of that information, and the systems where this information is stored, distributed, processed, and eventually destroyed. For example, by managing important external parties and their operations, analyzing their cybersecurity risk to our business operations, and reviewing the residual risk with business leaders to accept and manage each external party appropriately;
- protecting and securing our systems from attack with secure configuration standards and protective cybersecurity tools;
- detecting potential attacks through appropriate tools, including cybersecurity-related data collection and analysis to help identify potential attacks;
- responding to alerts from those tools with processes to verify whether there is a real incident and the severity of that incident using appropriate resources and team members, including establishing and exercising a Cybersecurity Incident Response Plan ("IRP") based on recognized industry practices, including NIST guidance; and
- establishing and exercising processes and procedures to recover from cybersecurity incidents.

Our IRP contains tools and guidance related to cybersecurity events and is designed to help coordinate our response to, and recovery from, cybersecurity incidents, and includes processes to triage, assess the severity of, escalate, contain, investigate, and remediate incidents as well as comply with applicable legal obligations. In addition, as part of our overall risk mitigation strategy, we also maintain cyber insurance coverage; however, such insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

We regularly engage external parties, inclusive of but not limited to, service vendors, consultants, independent privacy assessors, peer companies, industry groups, and governance experts to enhance our understanding and application of oversight of the cybersecurity landscape. For example, we provide an annual assessment of our cybersecurity program, completed by our third-party Chief Information Security Officer ("CISO"), to our Audit Committee for review and feedback. These external parties provide an industry perspective on appropriate risk management and investment in our cybersecurity efforts that is reviewed and approved by company management and the Board of Directors.

Based on an assessment using the previously described cybersecurity risk management process, we do not believe that there are any risks from known cybersecurity threats, including as a result of any prior cybersecurity incidents, that have materially affected or are reasonably likely to materially affect the Company, including its business strategy, results of operations or financial condition. See **"***Our business and operations may be materially adversely affected in the event of information technology system failures or security breaches, and the costs and consequences of implementing data protection measures could be significant."* in Part I, Item 1A. "*Risk Factors*" for additional information.

Cybersecurity Governance and Oversight

The Audit Committee of our Board of Directors provides direct oversight over cybersecurity risk. The Audit Committee receives and provides feedback on quarterly updates from management regarding cybersecurity and is notified between such updates regarding significant new cybersecurity threats or incidents, if any. As part of these quarterly updates to the Audit Committee, our Vice President of Information Technology presents any developments, emerging risks or key topics to the Audit Committee, including, among other things, the external threat environment, risk profile changes, training initiatives, the status of projects to strengthen cybersecurity, emerging global policies and regulations, cybersecurity technologies and industry practices, cyber readiness, results of third-party assessments, mitigation efforts and response plans. The full Board of Directors receives regular reports from the Chair of the Audit Committee, as well as periodic updates highlighting recent incidents throughout the industry and the emerging threat landscape.

Our Vice President of Information Technology leads an IT Security Team and has overall responsibility for the security program. The IT Security Team is responsible for leading company-wide cybersecurity strategy, policy, standards and processes. The IT Security Team works across the enterprise to assess and prepare our employees and third parties to manage cybersecurity risks and detect, investigate and respond to cybersecurity incidents. Our Vice President of Information Technology has over 25 years of information technology experience, including 23 years of leadership responsibility, and has substantial operational experience with cybersecurity policy, protection, incident response, and governance. We also utilize a third-party cybersecurity advisor to act as our CISO, supporting the Vice President of Information Technology. This fractional executive has extensive experience as a CISO and cybersecurity executive with over 25 years of expertise in designing, building, and operating transformational information security programs, is a Certified Information Systems Security Professional, and holds a Master of Science in Strategic Intelligence.

Further, our IRP establishes a corporate incident response team, which is responsible for providing oversight, direction, and governance of incident response policies and processes and is composed of certain company stakeholders, including our Chief Financial Officer, General Counsel, Vice President of Information Technology and our third-party CISO.

In an effort to deter and detect cyber threats, we provide a monthly cybersecurity awareness newsletter to all employees, including part-time and temporary contractors, which covers a range of timely and relevant topics. Past topics have included social engineering, phishing, password protection, confidential data protection, asset use and mobile security. The cybersecurity training and awareness programs function to remind employees of the importance of reporting all incidents quickly. We run frequent phishing tests to raise awareness of spam emails, the primary attack vectors for cyber threats and to further raise awareness of cyber threats. We provide annual training on employee responsibilities for protecting company information and data along with our overall compliance responsibility. Each October during cybersecurity awareness month in the U.S., we provide weekly updates on cybersecurity awareness and host a company-wide lunch and learn discussion of our cybersecurity program and the impact of cybersecurity on individuals as well as the company, with a data protection, cybersecurity and incident response and prevention training and compliance program.

Item 2. Properties

Our headquarters are located in Newton, Massachusetts, where we currently lease a total of 98,502 square feet of office and research space through September 30, 2025, which will be reduced to 52,224 square feet of solely office space from October 1, 2025 through September 30, 2030.

We also lease approximately 3,681 square feet of office space in Munich, Germany.

Item 3. Legal Proceedings

The information required by this Item is provided under "*Litigation*" in Note 12, "*Commitments and Contingencies",* of the consolidated financial statements included in Part II, Item 8 of this Annual Report on Form 10-K.

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, $0.0001 par value per share, began trading on the Nasdaq Global Select Market on November 6, 2013, where its prices are quoted under the symbol "KPTI."

Holders

As of February 14, 2025, there were nine holders of record of our common stock.

Dividends

We have never paid cash dividends on our common stock, and we do not expect to pay any cash dividends in the foreseeable future.

Recent Sales of Unregistered Securities

During the period covered by this Annual Report on Form 10-K, we did not issue any unregistered equity securities other than pursuant to transactions previously disclosed in our Current Reports on Form 8-K.

Item 6. [Reserved]

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

The following discussion of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes included elsewhere in this report. Some of the information contained in this discussion and analysis and set forth elsewhere in this report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review the section entitled "*Risk Factors*" in Part I - Item 1A of this report for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a commercial-stage pharmaceutical company pioneering novel cancer therapies and dedicated to the discovery, development and commercialization of first-in-class drugs directed against nuclear export for the treatment of cancer. Our scientific expertise is based upon an understanding of the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing and commercializing novel, small molecule Selective Inhibitor of Nuclear Export ("SINE") compounds that inhibit the nuclear export protein exportin 1 ("XPO1"). These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases with high unmet medical need. Our lead asset, XPOVIO® (selinexor), was the first oral XPO1 inhibitor to receive marketing approval, receiving its initial U.S. approval from the U.S. Food and Drug Administration ("FDA") in July 2019, and is currently approved and marketed in the U.S. for the following indications:

- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Approval in this indication was based on the results from the BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) trial;
- In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. Approval in this indication was based on the results from the STORM (**S**elinexor **T**reatment of **R**efractory **M**yeloma) trial; and
- For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma ("DLBCL"), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. This indication was approved under accelerated approval based on response rate and was based on the results from the SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) trial. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The commercialization of XPOVIO in the U.S. is currently supported by sales representatives, nurse liaisons, and a market access team, as well as KaryForward®, an extensive patient and healthcare provider support program. Our commercial efforts are also supplemented by patient support initiatives coordinated by our dedicated network of participating specialty pharmacy providers. We plan to continue to educate physicians, other healthcare providers and patients about XPOVIO's clinical profile and unique mechanism of action as we continue to expand XPOVIO use.

The commercialization of XPOVIO and NEXPOVIO® (selinexor) (the brand name for selinexor in Europe and the United Kingdom) outside of the U.S. is managed by our partners in their respective territories. XPOVIO/NEXPOVIO has received regulatory approval in various indications in over 45 countries outside the U.S. and is commercially available in a growing number of countries as our partners continue to secure reimbursement approvals.

Our primary focus is on marketing XPOVIO in its currently approved indications as well as developing and seeking the regulatory approval of selinexor as an oral agent targeting multiple high unmet need cancer indications, including our lead clinical programs in myelofibrosis and our other late-stage clinical programs in endometrial cancer and multiple myeloma. We plan to continue to conduct clinical trials and to seek additional approvals for the use of selinexor as a single agent or in combination with other oncology therapies to expand the patient populations that are eligible for treatment with selinexor. As announced in January 2024, further clinical development of our eltanexor program continues to remain on hold in an effort to focus our resources on our prioritized late-stage programs.

In May 2024, we entered into a series of transactions (the "Refinancing Transactions") to limit our aggregate indebtedness, extend the maturity of certain of our indebtedness and provide us with additional working capital. Pursuant to these transactions, we borrowed $100.0 million from existing lenders and certain entities managed by HealthCare Royalty Management, LLC ("HCRx") under a $100.0 million senior secured term loan facility (the "Term Loan") and used a portion of the proceeds of the Term Loan to repay obligations under our existing financing arrangement with HCRx pursuant to an amendment that made other changes to our

existing financing arrangement with HCRx. We also exchanged, pursuant to privately negotiated agreements, an aggregate principal amount of $148.0 million of our existing 3.00% unsecured convertible senior notes due 2025 (the "2025 Notes") for (i) $111.0 million aggregate principal amount of new 6.00% secured convertible senior notes due 2029 (the "2029 Notes") and (ii) warrants to purchase up to 45.8 million shares of our common stock. In addition, HCRx purchased $5.0 million aggregate principal amount of the 2029 Notes through satisfaction of $5.0 million of our existing obligations to HCRx. Please refer to Note 10 "*Long-Term Obligations*", to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K for additional details of the Refinancing Transactions.

As of December 31, 2024, we had an accumulated deficit of $1.6 billion. We had net losses of $76.4 million, $143.1 million, and $165.3 million for the years ended December 31, 2024, 2023 and 2022, respectively. We recognized total revenue of $145.2 million in 2024, including $112.8 million of XPOVIO net product revenue and $32.4 million of license revenue. License revenue included $15.0 million of revenue for the reimbursement of development related expenses from the Menarini Group ("Menarini"). As of December 31, 2024, we had $108.7 million in cash, cash equivalents and investments. Based on our current business plan and current capital resources, combined with the uncertainty regarding the availability of additional funding and considering our debt obligations, including a requirement to maintain cash, cash equivalents and investments of at least $25.0 million at all times, we have concluded that there is substantial doubt regarding our ability to continue as a going concern within one year after the date the accompanying consolidated financial statements are issued. See "*Liquidity, Capital Resources, and Going Concern*" below for a further discussion of our liquidity and the conditions that raise substantial doubt regarding our ability to continue as a going concern.

Critical Accounting Estimates

Our discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which we have prepared in accordance with U.S. generally accepted accounting principles. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported amounts of revenues and expenses during the reporting periods. We believe that the estimates and assumptions involved in the accounting policies described below may have the greatest potential impact on our consolidated financial statements and, therefore, consider these to be our critical accounting estimates. We evaluate our estimates and assumptions on an ongoing basis. Actual results may differ from these estimates under different assumptions and conditions. See Note 2, "*Summary of Significant Accounting Policies",* to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K for information about our significant accounting policies.

Product Revenue Reserves

We recognize product revenue, net of variable consideration related to certain allowances and accruals, when the customer takes control of the product, which is upon delivery to the customer. Revenue from product sales is recorded at the net sales price, which includes estimates of variable consideration for which reserves are reported. These reserves are based on the amounts earned, or to be claimed on the related sales, and are generally classified as reductions of accounts receivable (if the amount is payable to the customer) or a current liability (if the amount is payable to a party other than a customer). Certain amounts are known at the time of sale based on contractual terms and are recorded pursuant to the most likely amount method, which is the single most likely amount in a range of possible considerations. Other amounts are estimated pursuant to the expected value method, which is the sum of probability-weighted amounts in a range of possible consideration amounts. Relevant factors used in the expected value method include: current contractual and statutory requirements, specific known market events and trends, industry data, and forecasted customer buying and payment patterns. These reserves reflect our best estimates of the variable consideration based on the terms of the respective underlying contracts.

The estimates for our product revenue allowances and accruals are most significantly affected by chargebacks, which are contractual commitments to provide products to qualified healthcare entities at prices lower than the list prices charged to our customers who purchase XPOVIO directly from us, and rebates that represent discount obligations under government programs, including Medicaid, Medicare, the Department of Veterans Affairs, the Department of Defense, and others.

A 10% increase or decrease in these estimates would impact net product revenue by a corresponding increase or decrease of approximately $4.0 million.

License Agreements

We generate revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain of our products and product candidates.

At contract inception, we evaluate all goods or services in the agreement to determine if they are distinct. If they are not distinct, they are combined with other promised goods or services to create a bundle of promised goods or services that are distinct. Distinct goods or services and distinct bundles of goods or services are considered performance obligations. Optional future services where any additional consideration paid to us reflects their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations. Optional future services that are priced in a manner which provides the customer with a significant or incremental discount are considered performance obligations because they provide the customer with a material right.

We utilize judgment to estimate the transaction price at contract inception. We evaluate contingent milestones to determine if they should be included in the transaction price using the most likely amount method. Milestone payments that are not within our control, such as regulatory approvals, are not considered likely of being achieved until those approvals are received and are excluded from the transaction price using the most likely amount method. The transaction price is then allocated to each performance obligation on a relative standalone selling price basis, for which we recognize revenue as or when the performance obligations are satisfied. At the end of each reporting period, we re-evaluate our estimate of the transaction price including the probability of achieving milestone payments that may not be subject to a material reversal and adjust the transaction price if necessary. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license and other revenue in the period of adjustment.

Accrued Research and Development Costs

We estimate our accrued research and development costs by reviewing quotes and contracts, identifying services that have been performed on our behalf, and estimating the associated cost incurred for services performed when we have not yet been invoiced or otherwise notified of the actual cost. Most of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued research and development costs at each balance sheet date in our 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 costs include fees to be paid to contract research organizations ("CROs") and contract manufacturing organizations ("CMOs") in connection with research and development activities, as well as fees to be paid to investigative sites in connection with clinical studies, for which we have not yet been invoiced.

We base our expenses related to CROs and CMOs on our estimates of the services performed and efforts expended pursuant to quotes and contracts with CROs and CMOs that conduct research and development activities on our behalf. The payment 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 service providers will exceed the level of services performed and result in a prepayment. In accruing service fees, we estimate the time period over which the 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 estimates, we adjust the accrual or prepayment accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting amounts that are too high or too low in any particular period. To date, our estimates have not been materially different than amounts actually incurred.

Refinancing Transactions

Our estimated value of the gain on extinguishment of debt, the embedded derivatives in the 2029 Notes (as defined above) and the liability-classified common stock warrants related to the Refinancing Transactions, were valued using methodologies that incorporate certain unobservable inputs including (i) the volatility of our common stock price, (ii) our estimated credit spread and (iii) an estimate of when the warrants will be exercised based on an option pricing model. See Note 6, "*Fair Value Measurements",* and Note 10, "*Long-Term Obligations",* to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K for additional information.

Results of Operations

The following table summarizes our results of operations (in thousands, except for percentages):

	For the Years Ended December 31,			
	2024	2023	$ Change	% Change
Product revenue, net	$ 112,806	$ 112,011	$ 795	1%
License and other revenue	32,431	34,022	(1,591)	(5)%
Total revenue	145,237	146,033	(796)	(1)%
Operating expenses:				
Cost of sales	6,007	4,942	1,065	22%
Research and development	143,232	138,750	4,482	3%
Selling, general and administrative	115,441	131,881	(16,440)	(12)%
Loss from operations	(119,443)	(129,540)	10,097	(8)%
Other income (expense), net	43,078	(13,236)	56,314	(>100)%
Loss before income taxes	(76,365)	(142,776)	66,411	(47)%
Income tax provision	(57)	(323)	266	(82)%
Net loss	$ (76,422)	$ (143,099)	$ 66,677	(47)%

Product Revenue, net (in thousands, except for percentages)

	For the Years Ended December 31,			
	2024	2023	$ Change	% Change
Product revenue, net	$ 112,806	$ 112,011	$ 795	1%

Net product revenue from U.S. commercial sales of XPOVIO for the year ended December 31, 2024 was relatively consistent as compared to the year ended December 31, 2023. XPOVIO net product revenue was adversely impacted year-over-year by higher gross-to-net adjustments in 2024, driven primarily by 340B discounts and Medicare rebates. We expect net product revenue to increase in 2025 as compared to 2024 due to demand growth.

License and Other Revenue (in thousands, except for percentages)

	For the Years Ended December 31,			
	2024	2023	$ Change	% Change
Menarini	$ 28,014	$ 24,360	$ 3,654	15%
Antengene	1,680	2,713	(1,033)	(38)%
Other	2,737	6,949	(4,212)	(61)%
Total license and other revenue	$ 32,431	$ 34,022	$ (1,591)	(5)%

License and other revenue for the year ended December 31, 2024 decreased by $1.6 million as compared to the year ended December 31, 2023 primarily due to a decrease in milestone-related revenue from our other license agreements, offset by an increase in milestone-related and royalty revenue from Menarini. The license agreements with Menarini and Antengene Therapeutics Limited ("Antengene") are each defined and described in Note 5, "*License Agreements*", to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K.

We expect license and other revenue to slightly decrease in 2025 as compared to 2024 primarily due to a decrease in milestone-related revenue from our partners.

Operating Expenses (in thousands, except for percentages)

	For the Years Ended December 31,			
	2024	2023	$ Change	% Change
Cost of sales	$ 6,007	$ 4,942	$ 1,065	22%
Research and development	143,232	138,750	4,482	3%
Selling, general and administrative	115,441	131,881	(16,440)	(12)%
Total operating expenses	$ 264,680	$ 275,573	$ (10,893)	(4)%

Cost of Sales

Cost of sales for the year ended December 31, 2024 was relatively consistent with the year ended December 31, 2023. We expect cost of sales to remain relatively consistent in 2025 as compared to 2024.

Research and Development Expenses (in thousands, except for percentages)

	For the Years Ended December 31,			
	2024	2023	$ Change	% Change
Clinical trial and related costs:				
Selinexor in myelofibrosis	$ 32,093	$ 13,319	$ 18,774	>100%
Selinexor in multiple myeloma	17,320	15,287	2,033	13%
Selinexor in endometrial cancer	15,444	14,271	1,173	8%
Other programs	3,102	12,877	(9,775)	(76)%
Non-program specific clinical trial and related costs	7,522	9,939	(2,417)	(24)%
Total clinical trial and related costs	75,481	65,693	9,788	15%
Unallocated costs:				
Personnel costs	44,252	49,907	(5,655)	(11)%
Consulting, professional and other	18,658	16,621	2,037	12%
Stock-based compensation	4,841	6,529	(1,688)	(26)%
Total unallocated costs	67,751	73,057	(5,306)	(7)%
Total research and development expenses	$ 143,232	$ 138,750	$ 4,482	3%

At any one time, we have a number of ongoing clinical development programs that we are conducting independently or in collaboration with third parties. We track our external clinical trial and related costs on a program-by-program basis. Our major programs include our lead clinical programs in myelofibrosis and our other late-stage clinical programs in endometrial cancer and multiple myeloma. To the extent that external clinical trial and related costs are not attributable to a major program, they are included in "*Other programs*" and to the extent external clinical trial and related costs cannot be allocated to a specific program, they are included in "*Non-program specific clinical trial and related costs*." We also have unallocated research and development costs, which we do not track on a program-by-program basis. These costs represent expenses incurred across multiple programs or to support our general research and development operations.

Research and development expenses for the year ended December 31, 2024 increased by $4.5 million as compared to the year ended December 31, 2023. The $9.8 million increase in clinical trial and related costs was primarily due to increased activity in each of our ongoing Phase 3 trials, including increased purchases of comparator drugs. These increases were partially offset by a $9.8 million decrease in clinical trial and related costs in other programs. The decrease in personnel costs of $5.7 million was primarily due to a reduction in headcount and contractors for the year ended December 31, 2024 as compared to the year ended December 31, 2023 due to the realization of previously implemented cost reduction initiatives.

We expect our research and development expenses to decrease in 2025 as compared to 2024 due primarily to full enrollment in mid-2024 of our Phase 3 multiple myeloma study and decreased headcount costs, partially offset by an increase in expenses in connection with our ongoing Phase 3 trials in myelofibrosis and endometrial cancer.

Selling, General and Administrative Expenses (in thousands, except for percentages)

	For the Years Ended December 31,			
	2024	2023	$ Change	% Change
Personnel costs	$ 57,711	$ 66,465	$ (8,754)	(13)%
Consulting, professional and other costs	44,371	50,606	(6,235)	(12)%
Stock-based compensation	13,359	14,810	(1,451)	(10)%
Total selling, general and administrative expenses	$ 115,441	$ 131,881	$ (16,440)	(12)%

Selling, general and administrative expenses for the year ended December 31, 2024 decreased by $16.4 million as compared to the year ended December 31, 2023. The decrease in personnel costs of $8.8 million and the decrease in stock-based compensation of $1.5 million were primarily due to a reduction in headcount and contractors for the year ended December 31, 2024 as compared to the year ended December 31, 2023 due to our ongoing cost reduction initiatives. The decrease in consulting, professional and other costs of $6.2 million was primarily due to lower commercial-related activities in connection with cost optimization efforts during 2024.

We expect our selling, general and administrative expenses to slightly decrease in 2025 as compared to 2024 due to continued realization of previously implemented cost reduction initiatives.

Other Income (Expense), net (in thousands, except for percentages)

	For the Years Ended December 31,			
	2024	2023	$ Change	% Change
Interest expense	$ (37,422)	$ (23,823)	$ (13,599)	57%
Interest income	7,400	10,943	(3,543)	(32)%
Gain on extinguishment of debt	44,702	—	44,702	100%
Other income (expense), net	28,398	(356)	28,754	(>100)%
Total other income (expense), net	$ 43,078	$ (13,236)	$ 56,314	(>100)%

Other income (expense), net for the year ended December 31, 2024 increased by $56.3 million as compared to the year ended December 31, 2023, primarily due to a $44.7 million gain on extinguishment of debt from the Refinancing Transactions and a $28.7 million gain from the remeasurement of embedded derivatives and liability-classified common stock warrants, both of which are non-cash items. These gains were partially offset by an increase in interest expense related to the Term Loan and the 2029 Notes and a decrease in interest income resulting from lower investment balances in 2024 as compared to 2023.

We expect other income (expense), net to decrease in 2025 as compared to 2024 due to the $44.7 million gain on extinguishment of debt being a one-time, non-recurring item. We also expect increased interest expense in 2025 as compared to 2024 on the Term Loan and the 2029 Notes, as both of these instruments were issued in May 2024, and 2025 will include a full year of interest expense on these instruments. The future impact from remeasurements of the embedded derivatives and liability-classified common stock warrants will depend on a variety of factors, including movements in our stock price, and cannot be forecasted.

Results of Operations - Years Ended December 31, 2023 and 2022

Discussion and analysis of the results of operations for the year ended December 31, 2023 as compared to the results of operations for the year ended December 31, 2022 is included under the heading "*Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations*" in our Annual Report on Form 10-K for the year ended December 31, 2023 as filed with the SEC on February 29, 2024 ("2023 Form 10-K").

Liquidity, Capital Resources and Going Concern

Cash flows

We have historically financed our operations primarily through a combination of proceeds from (i) product revenue sales, (ii) public and private placements of equity securities, (iii) the issuance of convertible debt, (iv) a term loan, (v) our deferred royalty obligation, (vi) at the market offerings and (vii) business development activities. As of December 31, 2024, our principal source of liquidity was $108.7 million of cash, cash equivalents and investments. We have had recurring losses since inception and incurred a loss of $76.4 million for the year ended December 31, 2024.

We anticipate that we will continue to incur significant operating losses in the foreseeable future. Based on our current business plan and current capital resources, combined with the uncertainty regarding the availability of additional funding and considering our debt obligations, including a requirement to maintain cash, cash equivalents and investments of at least $25.0 million at all times, we have concluded that there is substantial doubt regarding our ability to continue as a going concern within one year after the date the accompanying consolidated financial statements are issued. We expect that our cash, cash equivalents and investments as of December 31, 2024 will be sufficient to fund our current operating plans and debt obligation requirements into the fourth quarter of 2025. See "*Liquidity, Capital Resources and Going Concern – Funding Requirements*" below and Note 1 "*Organization and Operations*" to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K for a further discussion of our liquidity and the conditions that raise substantial doubt regarding our ability to continue as a going concern.

The following table provides information regarding our cash flows (in thousands):

	For the Years Ended December 31,			
	2024	2023	$ Change	% Change
Net cash used in operating activities	$ (127,486)	$ (92,723)	$ (34,763)	37%
Net cash provided by investing activities	95,473	7,940	87,533	>100%
Net cash provided by financing activities	41,646	1,124	40,522	>100%
Effect of exchange rates on cash, cash equivalents and restricted cash	(11)	(34)	23	(68)%
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 9,622	$ (83,693)	$ 93,315	(>100)%

Net Cash Used in Operating Activities

The $34.8 million increase in net cash used in operating activities during the year ended December 31, 2024 as compared to the year ended December 31, 2023 was primarily driven by working capital changes, including the collection of $27.3 million of milestone payments from Antengene in 2023.

Net Cash Provided by Investing Activities

Net cash provided by investing activities increased by $87.5 million during the year ended December 31, 2024 as compared to the year ended December 31,2023. Proceeds from the maturities of investments decreased by $12.7 million in 2024, which was significantly offset by a decrease of $100.3 million in purchases of investments in 2024, due to liquidity needs to fund our operations.

Net Cash Provided by Financing Activities

The $40.5 million increase in net cash provided by financing activities during the year ended December 31, 2024 as compared to the year ended December 31, 2023 was primarily driven by $83.3 million of proceeds from the Term Loan, partially offset by a $40.5 million payment of our deferred royalty obligation to HCRx and a $2.6 million payment of debt issuance costs related to the Refinancing Transactions.

A discussion of changes in our financial condition for the year ended December 31, 2023 as compared to the year ended December 31, 2022 is included under the heading "*Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations*" in the 2023 Form 10-K.

Sources of Liquidity

On September 14, 2019, we and certain of our subsidiaries entered into the Revenue Interest Financing Agreement with HCRx, which was subsequently amended on June 23, 2021, August 1, 2023 and May 8, 2024 (the "Revenue Interest Agreement" and, as amended, the "Amended Revenue Interest Agreement"), pursuant to which, HCRx paid us a total of $135.0 million, less certain transaction expenses. For additional information on the Amended Revenue Interest Agreement, see Note 10, "*Long-Term Obligations*", to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K.

On May 8, 2024, we entered into a credit and guaranty agreement (the "Credit Agreement") with certain existing lenders and HCRx, which provides for a senior secured term loan facility of $100.0 million. For additional information, see Note 10, "*Long-Term Obligations*", to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K.

On February 17, 2023, we entered into an Open Market Sale Agreement (the "2023 Open Market Sale Agreement") with Jefferies LLC, as agent ("Jefferies"). Under the 2023 Open Market Sale Agreement, we may issue and sell shares of our common stock having an aggregate offering price of up to $100.0 million (the "Shares") from time to time through Jefferies. We did not sell any Shares under the 2023 Open Market Sales Agreement during the year ended December 31, 2024. As of December 31, 2024, $100.0 million of Shares was available for issuance and sale under the 2023 Open Market Sale Agreement.

During the year ended December 31, 2024, we received $19.6 million in milestone and upfront payments under our license and distribution arrangements pursuant to which we are entitled to receive additional milestone payments, if certain development goals and sales milestones are achieved, as well as royalties on future net sales of the licensed and sold products in the territories under such arrangements. In addition, under the Menarini Agreement, Menarini will reimburse us for 25% of all development related expenses we incur for selinexor from 2022 through 2025, provided that such reimbursements shall not exceed $15.0 million per calendar year. We received $15.0 million of reimbursements for development related expenses under the Menarini Agreement during the year ended December 31, 2024.

Commitments, Contingencies and Contractual Obligations

Operating Leases

We are party to an operating lease of office and research space in Newton, Massachusetts, which was amended in November 2024 and under which we currently lease a total of 98,502 square feet of research and office space through September 30, 2025, which will be reduced to 52,224 square feet of solely office space from October 1, 2025 through September 30, 2030. We expect to incur total lease costs of $10.9 million from January 1, 2025 to September 30, 2030.

Contractual Obligations

We have contractual obligations under our (i) 2025 Notes; (ii) Credit Agreement, (iii) 2029 Notes, and (iv) Amended Revenue Interest Agreement as disclosed in Note 10, "*Long-Term Obligations*", to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K.

Funding Requirements

We expect to continue to incur costs related to our clinical development programs as we continue to advance our lead clinical programs in myelofibrosis and our other late-stage clinical programs in endometrial cancer and multiple myeloma, as well as commercialization expenses related to sales, marketing, manufacturing and distribution of our approved products, to the extent that these functions are not the responsibility of our collaborators.

Identifying potential product candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete. In addition, our product candidates for which we receive marketing approval may not achieve commercial success. Our ability to become and remain profitable depends on our ability to generate revenue. There can be no assurance as to the amount or timing of any such revenue, and we may not achieve profitability for several years, if at all, as described more fully in the risk factor entitled "*We have incurred significant losses since inception, expect to continue to incur significant losses, and may never achieve or maintain profitability*," under the heading "*Risk Factors*" in this Annual Report on Form 10-K. 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. 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. 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 commercialization efforts.

Based on our current business plan and current capital resources, combined with the uncertainty regarding the availability of additional funding and considering our debt obligations, including a requirement to maintain cash, cash equivalents and investments of at least $25.0 million at all times, we have concluded that there is substantial doubt regarding our ability to continue as a going concern within one year after the date the accompanying consolidated financial statements are issued. See Note 1, "*Organization and Operations*", to the consolidated financial statements included under Part II, Item 8 of this Annual Report on Form 10-K for a further discussion of the conditions that raise substantial doubt regarding our ability to continue as a going concern. We currently expect that cash, cash equivalents and investments as of December 31, 2024 will be sufficient to fund our current operating plans and debt obligation requirements into the fourth quarter of 2025 while we continue to commercialize XPOVIO in the U.S. and continue the clinical trials of our product candidates. Our future long-term capital requirements will depend on many factors, as described more fully in the risk factor entitled "*We will need additional funding to achieve our business objectives. If we are unable to raise capital*

when needed or on acceptable terms, we would be forced to delay, reduce or eliminate our research and development programs and/or commercialization efforts," under the heading "*Risk Factors*" in this Annual Report on Form 10-K.

In addition to the expenses required to fund our operations described above, our funding requirements as of December 31, 2024 also include the following:

- Lease costs for our headquarters in Newton, Massachusetts of $10.9 million through September 30, 2030;
- Future obligations related to the 2025 Notes of $25.2 million through October 2025;
- Future obligations related to the 2029 Notes of $146.4 million through May 2029;
- Future obligations related to the Credit Agreement of $142.7 million through May 2028 in addition to our requirement to maintain cash, cash equivalents and investments of at least $25.0 million at all times; and
- Future royalty obligations to HCRx under the Amended Revenue Interest Agreement of $119.9 million by October 1, 2031.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. We had cash, cash equivalents and investments of $108.7 million as of December 31, 2024. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 100 basis point shift in interest rates would not have a material effect on the fair market value of our investment portfolio.

We do not believe our cash, cash equivalents and investments have significant risk of default or illiquidity. While we believe our cash, cash equivalents and investments do not contain excessive risk, we cannot provide absolute assurance that in the future our investments will not be subject to adverse changes in securities at one or more financial institutions that are in excess of federally insured limits. Given the potential instability of financial institutions, we cannot provide assurance that we will not experience losses on these deposits and investments.

We are also exposed to market risk related to changes in foreign currency exchange rates. We contract with contract research organizations and contract manufacturing organizations that are located in Canada, the United Kingdom and Europe, which are denominated in foreign currencies. We also contract with a number of clinical trial sites outside of the U.S., and our budgets for those studies are frequently denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these agreements. We do not currently hedge our foreign currency exchange rate risk.

Item 8. Financial Statements and Supplementary Data

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K and are incorporated herein by reference. An index of those financial statements is found in Item 15 of Part IV of this Annual Report on Form 10-K.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

We have established disclosure controls and procedures designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the rules and forms prescribed by the Securities and Exchange Commission and is accumulated and communicated to management, including the principal executive officer (our President and Chief Executive Officer) and principal financial officer (our Executive Vice President, Chief Financial Officer and Treasurer), to allow timely decisions regarding required disclosure.

Our management, under the supervision and with the participation of our President and Chief Executive Officer and Executive Vice President, Chief Financial Officer and Treasurer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of the end of the period covered by this Annual Report on Form 10-K. Management recognizes that any disclosure controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives. Our disclosure controls and procedures have been designed to provide reasonable assurance of achieving their objectives. Based on such evaluation, our President and Chief Executive Officer and Executive Vice President, Chief Financial Officer and Treasurer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2024.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules13a-15(f) and15d-15(f) of the Exchange Act. 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 policies or procedures may deteriorate. Our internal control over financial reporting is a process designed under the supervision of our principal executive officer and principal financial officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external reporting purposes in accordance with U.S. generally accepted accounting principles.

Under the supervision and with the participation of management, including our principal executive officer and principal financial officer we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the 2013 framework in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on our evaluation under that framework, management concluded that our internal control over financial reporting was effective as of December 31, 2024.

Our independent registered public accounting firm that audited the financial statements included in this Annual Report on Form 10-K has issued an attestation report on our internal control over financial reporting, which is included below.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2024 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Karyopharm Therapeutics Inc.

Opinion on Internal Control Over Financial Reporting

We have audited Karyopharm Therapeutics Inc.'s internal control over financial reporting as of December 31, 2024, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), (the COSO criteria). In our opinion, Karyopharm Therapeutics Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2024, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the 2024 consolidated financial statements of the Company and our report dated February 19, 2025 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the 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 audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed 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. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) 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 the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

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.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 19, 2025

Item 9B. Other Information

Director and Officer Trading Arrangements

A portion of the compensation of our directors and officers (as defined in Rule 16a-1(f) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")) is in the form of equity awards and, from time to time, directors and officers engage in open-market transactions with respect to the securities acquired pursuant to such equity awards or other securities of our company, including to satisfy tax withholding obligations when equity awards vest or are exercised, and for diversification or other personal reasons.

Transactions in our securities by directors and officers are required to be made in accordance with our Insider Trading Policy, which requires that the transactions be in accordance with applicable U.S. federal securities laws that prohibit trading while in possession of material nonpublic information. Rule 10b5-1 under the Exchange Act provides an affirmative defense that enables directors and officers to prearrange transactions in our securities in a manner that avoids concerns about initiating transactions while in possession of material nonpublic information.

During the fourth quarter of 2024, none of our directors or officers adopted or terminated a Rule 10b5-1 trading arrangement or a non-Rule 10b5-1 trading arrangement (as defined in Item 408(c) of Regulation S-K).

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K and is incorporated by reference from our definitive proxy statement relating to our 2025 annual meeting of stockholders, pursuant to Regulation 14A of the Exchange Act, which we refer to as our 2025 Proxy Statement. We expect to file our 2025 Proxy Statement with the SEC within 120 days of December 31, 2024.

Item 10. Directors, Executive Officers and Corporate Governance

Information regarding our directors, including the audit committee and audit committee financial experts, insider trading policies and procedures and compliance with Section 16(a) of the Exchange Act, if applicable, will be included in our 2025 Proxy Statement and is incorporated herein by reference. Information regarding our executive officers is set forth in "*Business - Information about our Executive Officers*" in Part I, Item 1 of this Annual Report on Form 10-K.

We have adopted a Code of Business Conduct and Ethics for all of our directors, officers and employees as required by Nasdaq governance rules and as defined by applicable SEC rules. Stockholders may locate a copy of our Code of Business Conduct and Ethics on our website at www.karyopharm.com or request a copy without charge from:

Karyopharm Therapeutics Inc.
Attention: Investor Relations
85 Wells Avenue, 2nd Floor
Newton, MA 02459

We will post to our website any amendments to the Code of Business Conduct and Ethics and any waivers that are required to be disclosed by the rules of either the SEC or Nasdaq.

Item 11. Executive Compensation

The information required by this Item 11 of Form 10-K regarding executive compensation will be included in our 2025 Proxy Statement and, other than the information required by Item 402(v) of Regulation S-K, is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item 12 of Form 10-K regarding security ownership of certain beneficial owners and management and securities authorized for issuance under equity compensation plans will be included in our 2025 Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item 13 of Form 10-K regarding certain relationships and related transactions and director independence will be included in our 2025 Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services

The information required by this Item 14 of Form 10-K regarding principal accountant fees and services will be included in our 2025 Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Financial Statements

The financial statements listed below are filed as a part of this Annual Report on Form 10-K.

(a)(2) Financial Statement Schedules

All financial schedules have been omitted because the required information is either presented in the consolidated financial statements or the notes thereto or is not applicable or required.

(a)(3) Exhibits

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K and are incorporated herein.

Item 16. Form 10-K Summary

None.

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Karyopharm Therapeutics Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Karyopharm Therapeutics Inc. (the Company) as of December 31, 2024 and 2023, the related consolidated statements of operations, comprehensive loss, stockholders' deficit and cash flows for each of the three years in the period ended December 31, 2024, 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, 2024 and 2023, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2024, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2024, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), and our report dated February 19, 2025 expressed an unqualified opinion thereon.

The Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the financial statements, the Company has incurred significant operating losses since inception, expects to incur significant operating losses for the foreseeable future, and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

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 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. 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 Matter

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 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 accounts or disclosures to which it relates.

Accrued Research and Development Costs

Description of the Matter

The Company's accrued research and development costs totaled $26.7 million at December 31, 2024. As discussed in Note 2 to the consolidated financial statements, the Company's accrued research and development costs are recognized based on reviewing quotes and contracts, identifying services that have been performed on the Company's behalf and estimating the associated costs incurred for services performed when invoices have not yet been received. Payments for these activities are based on the terms of individual arrangements, which vary from contract to contract, and may differ from the pattern of costs incurred and are reflected on the consolidated balance sheet as accrued expenses when expenses incurred exceed payments to date.

Auditing the Company's accrued research and development costs is especially challenging due to the significant volume of information received from service providers that conduct research and development activities on the Company's behalf. While the Company's estimates of accrued research and development costs are primarily based on information received related to each study or ongoing work order from its service providers, the Company may need to make an estimate for additional costs incurred. Finally, due to the duration of certain of the Company's ongoing research and development activities and the timing of invoicing received from service providers, the actual amounts incurred are not typically known by the report date.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design, and tested the operating effectiveness of the controls over the Company's process for recording accrued research and development costs. These procedures included controls over management's review of inputs used, as well as the completeness and accuracy of the underlying data, in calculating the accrual.

To test accrued research and development costs, our audit procedures included, among others, testing the accuracy and completeness of the underlying data used to calculate accrued research and development costs, as well as evaluating the assumptions used by management. To assess the nature and extent of services incurred, we corroborated the progress of clinical trials with the Company's research and development personnel that oversee the clinical trials and obtained information from service providers regarding costs incurred to date. We also tested subsequent invoices received and inspected the Company's contracts with service providers and any pending change orders to assess the effect on the accrual.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2014.
Boston, Massachusetts
February 19, 2025

Karyopharm Therapeutics Inc.
Consolidated Balance Sheets

(in thousands, except per share amounts)

	December 31, 2024	December 31, 2023
Assets		
Current assets:		
Cash and cash equivalents	$ 62,476	$ 52,231
Investments	46,236	139,212
Accounts receivable, net	30,766	26,962
Inventory	4,739	3,043
Prepaid expenses and other current assets	12,245	11,813
Restricted cash	30	660
Total current assets	156,492	233,921
Property and equipment, net	400	606
Operating lease right-of-use assets	5,884	4,276
Restricted cash	308	301
Other assets	1,334	1,334
Total assets	$ 164,418	$ 240,438
Liabilities and stockholders' deficit		
Current liabilities:		
Accounts payable	$ 5,107	$ 3,123
Accrued expenses	60,652	61,394
Convertible senior notes due 2025	24,426	—
Operating lease liabilities	438	3,308
Other current liabilities	1,641	1,654
Total current liabilities	92,264	69,479
Convertible senior notes due 2025	—	170,919
Convertible senior notes due 2029	68,345	—
Senior secured term loan	94,603	—
Deferred royalty obligation	73,499	132,479
Common stock warrants	12,582	—
Operating lease liabilities, net of current portion	6,712	2,789
Other liabilities	2,430	978
Total liabilities	350,435	376,644
Stockholders' deficit:		
Preferred stock, $0.0001 par value; 5,000 shares authorized; none issued and outstanding	—	—
Common stock, $0.0001 par value; 400,000 shares authorized; 126,201 and 114,915 shares issued and outstanding as of December 31, 2024 and December 31, 2023, respectively	13	12
Additional paid-in capital	1,377,786	1,350,981
Accumulated other comprehensive loss	(356)	(161)
Accumulated deficit	(1,563,460)	(1,487,038)
Total stockholders' deficit	(186,017)	(136,206)
Total liabilities and stockholders' deficit	$ 164,418	$ 240,438

The accompanying notes are an integral part of these consolidated financial statements.

Karyopharm Therapeutics Inc.
Consolidated Statements of Operations

(in thousands, except per share amounts)

	For the Years Ended December 31,		
	2024	2023	2022
Revenues:			
Product revenue, net	$ 112,806	$ 112,011	$ 120,445
License and other revenue	32,431	34,022	36,629
Total revenue	145,237	146,033	157,074
Operating expenses:			
Cost of sales	6,007	4,942	5,213
Research and development	143,232	138,750	148,662
Selling, general and administrative	115,441	131,881	145,401
Total operating expenses	264,680	275,573	299,276
Loss from operations	(119,443)	(129,540)	(142,202)
Other income (expense):			
Interest income	7,400	10,943	2,359
Interest expense	(37,422)	(23,823)	(24,996)
Gain on extinguishment of debt	44,702	—	—
Other income (expense), net	28,398	(356)	(83)
Total other income (expense), net	43,078	(13,236)	(22,720)
Loss before income taxes	(76,365)	(142,776)	(164,922)
Income tax provision	(57)	(323)	(369)
Net loss	$ (76,422)	$ (143,099)	$ (165,291)
Basic net loss per share (Note 2)	$ (0.63)	$ (1.25)	$ (2.02)
Diluted net loss per share (Note 2)	$ (0.93)	$ (1.25)	$ (2.02)
Weighted-average number of common shares outstanding used to compute basic net loss per share	121,863	114,221	81,871
Weighted-average number of common shares outstanding used to compute diluted net loss per share	126,809	114,221	81,871

The accompanying notes are an integral part of these consolidated financial statements.

Karyopharm Therapeutics Inc.
Consolidated Statements of Comprehensive Loss

(in thousands)

	For the Years Ended December 31,		
	2024	2023	2022
Net loss	$ (76,422)	$ (143,099)	$ (165,291)
Other comprehensive income (loss)			
Unrealized gain (loss) on investments	133	278	(341)
Foreign currency translation adjustment	(328)	199	(488)
Comprehensive loss	$ (76,617)	$ (142,622)	$ (166,120)

The accompanying notes are an integral part of these consolidated financial statements.

Karyopharm Therapeutics Inc.
Consolidated Statements of Stockholders' Deficit

(in thousands)

	Common Shares		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount				
Balance as of December 31, 2021	75,746	$ 8	$ 1,098,776	$ 191	$ (1,178,648)	$ (79,673)
Vesting of restricted stock	957	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	726	—	3,977	—	—	3,977
Stock-based compensation expense	—	—	35,399	—	—	35,399
Issuance of common stock, net of issuance costs	35,784	4	189,757	—	—	189,761
Unrealized loss on investments	—	—	—	(341)	—	(341)
Foreign currency cumulative translation adjustment	—	—	—	(488)	—	(488)
Net loss	—	—	—	—	(165,291)	(165,291)
Balance as of December 31, 2022	113,213	12	1,327,909	(638)	(1,343,939)	(16,656)
Vesting of restricted stock	1,054	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	648	—	1,124	—	—	1,124
Stock-based compensation expense	—	—	21,709	—	—	21,709
Issuance of common stock warrants	—	—	239	—	—	239
Unrealized gain on investments	—	—	—	278	—	278
Foreign currency cumulative translation adjustment	—	—	—	199	—	199
Net loss	—	—	—	—	(143,099)	(143,099)
Balance as of December 31, 2023	114,915	12	1,350,981	(161)	(1,487,038)	(136,206)
Vesting of restricted stock	2,436	—	—	—	—	—
Shares issued under the employee stock purchase plan	1,978	—	1,452	—	—	1,452
Issuance of common stock for financial advisory fee	6,872	1	6,927	—	—	6,928
Stock-based compensation expense	—	—	18,426	—	—	18,426
Unrealized gain on investments	—	—	—	133	—	133
Foreign currency cumulative translation adjustment	—	—	—	(328)	—	(328)
Net loss	—	—	—	—	(76,422)	(76,422)
Balance as of December 31, 2024	126,201	$ 13	$ 1,377,786	$ (356)	$ (1,563,460)	$ (186,017)

The accompanying notes are an integral part of these consolidated financial statements.

Karyopharm Therapeutics Inc.
Consolidated Statements of Cash Flows

(in thousands)

	For the Years Ended December 31,		
	2024	**2023**	**2022**
Operating activities			
Net loss	$ (76,422)	$ (143,099)	$ (165,291)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	18,426	21,709	35,399
Depreciation and amortization	340	530	621
Amortization of debt issuance costs and discounts	6,369	814	812
Net amortization of premiums and discounts on investments	(2,504)	(4,098)	(825)
Gain on extinguishment of debt	(44,702)	—	—
Change in fair value of embedded derivatives and common stock warrants	(28,691)	—	(281)
Changes in operating assets and liabilities:			
Accounts receivable, net	(3,804)	20,124	(5,084)
Inventory	(1,696)	1,181	(118)
Prepaid expenses and other assets	(432)	6,674	(5,782)
Operating lease right-of-use assets	(1,608)	1,962	1,677
Accounts payable	1,984	350	1,170
Accrued expenses and other liabilities	4,201	4,002	(9,536)
Operating lease liabilities	1,053	(2,872)	(2,316)
Net cash used in operating activities	(127,486)	(92,723)	(149,554)
Investing activities			
Proceeds from maturities of investments	154,437	167,091	121,878
Purchases of investments	(58,822)	(159,151)	(226,016)
Purchases of property and equipment	(142)	—	(118)
Net cash provided by (used in) investing activities	95,473	7,940	(104,256)
Financing activities			
Proceeds from issuance of senior secured term loan	83,300	—	—
Proceeds from issuance of common stock, net of issuance costs	—	—	189,761
Proceeds from the exercise of stock options and shares issued under the employee stock purchase plan	1,452	1,124	3,977
Payment of debt issuance costs	(2,588)	—	—
Payment of deferred royalty obligation	(40,518)	—	—
Net cash provided by financing activities	41,646	1,124	193,738
Effect of exchange rates on cash, cash equivalents and restricted cash	(11)	(34)	(488)
Net increase (decrease) in cash, cash equivalents and restricted cash	9,622	(83,693)	(60,560)
Cash, cash equivalents and restricted cash at beginning of period	53,192	136,885	197,445
Cash, cash equivalents and restricted cash at end of period	$ 62,814	$ 53,192	$ 136,885
Reconciliation of cash, cash equivalents and restricted cash reported within the consolidated balance sheets			
Cash and cash equivalents	$ 62,476	$ 52,231	$ 135,188
Short-term restricted cash	30	660	1,064
Long-term restricted cash	308	301	633
Total cash, cash equivalents and restricted cash	$ 62,814	$ 53,192	$ 136,885
Supplemental disclosures:			
Cash paid for interest on deferred royalty obligation	$ 21,475	$ 16,053	$ 29,273
Cash paid for interest on convertible debt and term loan	$ 17,120	$ 5,175	$ 5,175
Cash paid for amounts included in the measurement of operating lease liabilities	$ 3,493	$ 3,718	$ 3,447
Lease liabilities arising from obtaining right-of-use assets	$ 3,602	$ —	$ —
Convertible senior notes due 2029 issued with warrants to purchase 45,776 shares of common stock in exchange for a $148.0 million reduction of convertible senior notes due 2025	$ 111,000	$ —	$ —
Senior secured term loan issued in exchange for a $14.7 million reduction of deferred royalty obligation	$ 15,000	$ —	$ —
Issuance of common stock used to settle a financial advisory fee related to financing activities	$ 7,697	$ —	$ —
Convertible senior notes due 2029 issued in exchange for a $5.0 million reduction of deferred royalty obligation	$ 5,000	$ —	$ —

The accompanying notes are an integral part of these consolidated financial statements.

Karyopharm Therapeutics Inc.
Notes to Consolidated Financial Statements

1. Organization and Operations

We are a commercial-stage pharmaceutical company pioneering novel cancer therapies and dedicated to the discovery, development and commercialization of first-in-class drugs directed against nuclear export for the treatment of cancer. Our scientific expertise is based upon an understanding of the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing and commercializing novel, small molecule Selective Inhibitor of Nuclear Export compounds that inhibit the nuclear export protein exportin 1. Our primary focus is on marketing XPOVIO® (selinexor) in its currently approved indications, as well as developing and seeking the regulatory approval of selinexor as an oral agent targeting multiple high unmet cancer indications, including our lead clinical programs in myelofibrosis and our other late-stage clinical programs in endometrial cancer and multiple myeloma. We were incorporated in Delaware on December 22, 2008 and have a principal place of business in Newton, Massachusetts.

Our lead asset, XPOVIO, received its initial U.S. approval from the U.S. Food and Drug Administration (the "FDA") in July 2019 and is currently approved and marketed for the following indications: (i) in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; (ii) in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody; and (iii) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma ("DLBCL"), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy. The commercialization of XPOVIO and NEXPOVIO® (selinexor)(the brand name for selinexor in Europe and the United Kingdom) outside of the U.S. is managed by our partners in their respective territories. XPOVIO/NEXPOVIO has received regulatory approval in various indications in over 45 countries outside the U.S. and is commercially available in a growing number of countries as our partners continue to secure reimbursement approvals.

We have historically financed our operations primarily through a combination of proceeds from (i) product revenue sales, (ii) public and private placements of equity securities, (iii) the issuance of convertible debt, (iv) a term loan, (v) our deferred royalty obligation, (vi) at the market offerings and (vii) business development activities. As of December 31, 2024, we had an accumulated deficit of $1.6 billion. We have incurred significant operating losses since our inception and we anticipate that we will continue to incur significant operating losses to maintain our research and development programs, including as we continue to develop and seek regulatory approval of selinexor for multiple cancer indications, and to support our continued operations. As a result, our continued operations are dependent on our ability to raise additional funding and marketing XPOVIO in its currently approved indications. Based on our current business plan and current capital resources, combined with the uncertainty regarding the availability of additional funding and considering our debt obligations, including a requirement to maintain cash, cash equivalents and investments of at least $25.0 million at all times, we have concluded that there is substantial doubt regarding our ability to continue as a going concern within one year after the date these consolidated financial statements are issued. We plan to address the conditions that raise substantial doubt regarding our ability to continue as a going concern by, among other things, obtaining additional funding through equity offerings, debt financings and refinancings, collaborations, strategic alliances and/or licensing arrangements. However, there is no assurance that such additional funding will be available on terms acceptable to us, or at all. We may also be required to reduce our current spending requirements where possible.

If we utilize our capital resources more quickly than anticipated or are unable to obtain additional funding, we may have to significantly curtail, delay, reduce or eliminate one or more of our research and development programs or any current or future commercialization efforts for one or more of our products or product candidates, which could materially adversely affect our business, financial condition, and results of operations. If we are unable to continue as a going concern, we may have to liquidate our assets and may receive less than the value at which those assets are carried on our financial statements, and it is likely that investors will lose all or part of their investment. If we seek additional financing to fund our business activities in the future, investors or other financing sources may be unwilling to provide funding to us on commercially reasonable terms, if at all. The accompanying consolidated financial statements do not include any adjustments to the carrying amounts and classification of assets and liabilities that may be necessary if we were unable to continue as a going concern.

2. Summary of Significant Accounting Policies

Basis of Presentation and Principles of Consolidation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP") and include the accounts of (i) Karyopharm Therapeutics Inc., (ii) Karyopharm Securities Corp. ("KSC"), our wholly-owned Massachusetts corporation incorporated in December 2013 and dissolved in October 2024, (iii) Karyopharm Europe GmbH, our wholly-owned German limited liability company, incorporated in September 2014, and (iv) Karyopharm Israel Ltd., our wholly-owned Israeli subsidiary formed in June 2018. All intercompany balances and transactions have been eliminated in consolidation.

Recent Accounting Pronouncements

In December 2023, the Financial Accounting Standards Board issued Accounting Standards Update 2023-09, *Improvements to Income Tax Disclosures*, which requires entities to disclose disaggregated information about their effective tax rate reconciliation as well as expanded information on income taxes paid by jurisdiction. The disclosure requirements will be applied on a prospective basis, with the option to apply them retrospectively. The standard is effective for fiscal years beginning after December 15, 2024. We are currently evaluating the disclosure requirements related to this new standard.

Segment Information

Operating segments are defined as components of an enterprise whose operating results are regularly reviewed by the Chief Operating Decision Maker ("CODM") to allocate resources and assess performance. We view our operations and manage our business as a single operating segment, which is the business of discovering, developing and commercializing drugs to treat cancer. All our revenue and all our long-lived assets are attributable to the United States and to our single operating segment.

Our CODM is our Chief Executive Officer who uses net loss as reported on the consolidated statements of operations to monitor budget versus actual results and to ensure we have sufficient capital resources to develop and seek regulatory approval of our product candidates. The following table presents the significant revenue and expense categories in our single operating segment:

	For the Years Ended December 31,		
	2024	2023	2022
Revenue from external customers	$ 145,237	$ 146,033	$ 157,074
Cost of sales (1)	(5,780)	(4,572)	(4,987)
Research and development expenses (2)	(144,756)	(138,135)	(142,046)
Commercial expenses (2)	(50,875)	(60,640)	(65,401)
General and administrative expenses (2)	(44,843)	(50,517)	(51,443)
Other segment income (expenses) (3)	24,595	(35,268)	(58,488)
Net loss of our single operating segment	$ (76,422)	$ (143,099)	$ (165,291)

(1) Excludes stock-based compensation expense

(2) Excludes stock-based compensation expense and the effects of certain allocations of certain expenses

(3) Includes total other income (expense), net on the consolidated statements of operations, income tax provision, and stock-based compensation expense

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period.

On an ongoing basis, we evaluate our estimates, including estimates related to our net product revenue, license and other revenue, clinical trial accruals, stock-based compensation expense, interest expense on our deferred royalty obligation, embedded derivative liabilities, liability-classified common stock warrants, valuation allowances, and other reported amounts of expenses during the reported period. We base our estimates on historical experience and other market-specific or relevant assumptions that we believe to be reasonable under the circumstances. Although we regularly assess these estimates, actual results could differ from those estimates. Changes in estimates are recorded in the period in which they become known.

Concentrations of Credit Risk and Off-Balance Sheet Risk

Financial instruments which potentially subject us to credit risk consist primarily of cash, cash equivalents and investments. We hold these investments in highly rated financial institutions, and, by policy, limit the amounts of credit exposure to any one financial institution. These amounts at times may exceed federally insured limits. We have not experienced any credit losses in such accounts and do not believe we are exposed to any significant credit risk on these funds. We have no off-balance sheet concentrations of credit risk.

The following table summarizes customers that represent 10% or greater of our consolidated total revenue:

	For the Years Ended December 31,		
	2024	2023	2022
Customer A	24%	35%	32%
Customer B	25%	23%	24%
Customer C	23%	13%	13%
Menarini	19%	17%	10%

The following table summarizes customers with amounts due that represent 10% or greater of our consolidated accounts receivable, net balance:

	As of December 31,	
	2024	2023
Customer A	25%	31%
Customer B	33%	22%
Customer C	19%	11%
Customer D	14%	<10%
Menarini	<10%	17%

Fair Value Measurements

Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. We disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. The fair value hierarchy prioritizes valuation inputs based on the observable nature of those inputs. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value and is not a measure of credit quality. The hierarchy defines three levels of valuation inputs:

Level 1 inputs: Quoted prices in active markets for identical assets or liabilities

Level 2 inputs: Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly

Level 3 inputs: Unobservable inputs that reflect our own assumptions about the assumptions market participants would use in pricing the asset or liability.

Cash and Cash Equivalents

Cash and cash equivalents consist primarily of demand deposit accounts and deposits in short-term money market funds. Cash equivalents are stated at cost, which approximates fair value. We consider all highly liquid investments with maturities of three months or less from the date of purchase to be cash equivalents. We do not hold any money market funds with significant liquidity restrictions that would be required to be excluded from cash equivalents.

Investments

We determine the appropriate classification of our investments at the time of purchase. All of our investments are reported as short-term as they are available for use during the normal cycle of business. We review any investment when its fair value is less than its amortized cost and when evidence indicates that the investment's carrying amount is not recoverable within a reasonable period. We evaluate whether the decline in fair value has resulted from credit losses or other factors. In making this assessment, we consider the extent to which fair value is less than amortized cost, any changes to the rating of the security by a rating agency, and adverse

conditions specifically related to the security, among other factors. If this assessment indicates that a credit loss exists and if the present value of cash flows expected to be collected is less than the amortized cost basis, an allowance is recorded on our consolidated balance sheet, limited by the amount that the fair value is less than the amortized cost basis. Any impairment that is not related to a credit loss is recognized in other comprehensive income (loss).

Changes in the allowance for credit losses are recorded as a provision for (or reversal of) credit loss expense. Losses are charged against the allowance when we believe the uncollectability of an investment is confirmed or when either of the criteria regarding intent or requirement to sell is met.

Accounts Receivable

Amounts are recorded as accounts receivable when our right to consideration is unconditional other than the passage of time. Accounts receivable consists of amounts due from customers, net of customer allowances for cash discounts and chargebacks. Our contracts with customers have standard payment terms that generally require payment within 31 to 68 days. We analyze accounts for collectability and periodically evaluate the creditworthiness of our customers. We determined an allowance for credit losses was not material as of December 31, 2024 and 2023 as we have had no bad debt write-offs to date and we do not currently have credit issues with any customers.

Accrued Research and Development Costs

We estimate our accrued research and development costs by reviewing quotes and contracts, identifying services that have been performed on our behalf, and estimating the associated cost incurred for services performed when we have not yet been invoiced or otherwise notified of the actual cost. Most of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued research and development costs at each balance sheet date in our 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 costs include fees to be paid to contract research organizations ("CROs"), and contract manufacturing organizations ("CMOs") in connection with research and development activities as well as fees to be paid to investigative sites in connection with clinical studies, for which we have not yet been invoiced.

We base our expenses related to CROs and CMOs on our estimates of the services performed and efforts expended pursuant to quotes and contracts with CROs and CMOs that conduct research and development activities on our behalf. The payment 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 service providers will exceed the level of services performed and result in a prepayment. In accruing service fees, we estimate the time period over which the 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 estimates, we adjust the accrual or prepayment accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting amounts that are too high or too low in any particular period. To date, our estimates have not been materially different than amounts actually incurred.

Deferred Royalty Obligation

We treat the debt obligation to HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. ("HCRx"), as discussed further in Note 10, "*Long-Term Obligations"*, as a deferred royalty obligation, amortized using the effective interest rate method over the estimated life of the revenue streams. We recognize interest expense thereon using the effective rate, which is based on our current estimates of future revenues over the life of the arrangement. We periodically assess our expected revenues using internal projections, impute interest on the carrying value of the deferred royalty obligation, and record interest expense using the imputed effective interest rate. To the extent our estimates of future revenues are greater or less than previous estimates or the estimated timing of such payments is materially different than previous estimates, we will account for any such changes by adjusting the effective interest rate on a prospective basis, which will adjust future interest expense with a corresponding impact to the classification of our deferred royalty obligation. The assumptions used in determining the expected repayment term of the deferred royalty obligation and amortization period of the issuance costs requires that we make estimates that could impact the short-term and long-term classification of such costs, as well as the period over which such costs will be amortized.

Embedded Derivatives

Embedded derivatives that require bifurcation are separated from the host debt instrument and are measured at fair value at the end of each reporting period. See Note 6, "*Fair Value Measurements",* for additional detail on the valuation methodology. Changes in fair value are recognized as a component of other income (expense), net on our consolidated statements of operations. Embedded derivatives are reported in the same line as the host debt instrument on the consolidated balance sheets.

Common Stock Warrants

We classify our common stock warrants in stockholder's equity if they allow for settlement only in shares of our common stock, are indexed to our common stock, and meet the criteria for equity classification. Common stock warrants that do not meet the criteria for equity classification are classified as liabilities and are measured at fair value at the end of each reporting period. See Note 6, "*Fair Value Measurements",* for additional detail on the valuation methodology.

Revenue Recognition

To determine revenue recognition, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfy a performance obligation. At contract inception, we assess whether the goods or services promised within a contract with a customer are distinct and, therefore, represent a separate performance obligation. Goods or services that are determined not to be distinct are combined with other promised goods and services until a distinct bundle is identified. We then determine the transaction price, which is the total amount of consideration we expect to receive from a customer in exchange for the promised goods or services and includes an estimate of any variable consideration in the contract. We then allocate the transaction price to each performance obligation and recognize the associated revenue when (or as) our customer obtains control of the goods or services within the performance obligation.

Incremental costs of obtaining a contract with a customer are capitalized and amortized consistent with the pattern of transferring the goods or services to which the cost relates when the expected amortization period of the asset is greater than one year. Incremental costs are expensed as incurred if the expected amortization period of the asset that we would have recognized is one year or less.

Product Revenue Recognition

We ship XPOVIO in the U.S. to specialty pharmacies and specialty distributors, collectively referred to as our customers, under a limited number of distribution arrangements with such third parties. Our specialty pharmacy customers resell XPOVIO directly to patients, while our specialty distributor customers resell XPOVIO to healthcare entities, who then resell XPOVIO to patients. We also enter into certain arrangements with group purchasing organizations and/or other payors that provide for government mandated and/or privately negotiated rebates, chargebacks, and discounts with respect to the purchase of our products.

Each unit of XPOVIO that is ordered by our customers represents a distinct performance obligation that is completed when control of the product is transferred to the customer. Accordingly, we recognize product revenue when the customer obtains control of our product, which occurs at a point in time, upon delivery pursuant to our agreements with our customers. If taxes are collected from customers relating to product sales and remitted to governmental authorities, they are excluded from revenue.

Revenue from product sales is recorded at the net sales price, which includes estimates of variable consideration for which reserves are reported. These reserves, as detailed below, are based on the amounts earned, or to be claimed on the related sales, and are generally classified as reductions of accounts receivable (if the amount is payable to the customer) or a current liability (if the amount is payable to a party other than a customer). Certain amounts are known at the time of sale based on contractual terms and are recorded pursuant to the most likely amount method, which is the single most likely amount in a range of possible considerations. Other amounts are estimated pursuant to the expected value method, which is the sum of probability-weighted amounts in a range of possible consideration amounts. Relevant factors used in the expected value method include: current contractual and statutory requirements, specific known market events and trends, industry data, and forecasted customer buying and payment patterns. These reserves reflect our best estimates of the variable consideration based on the terms of the respective underlying contracts.

The following are the components of variable consideration related to product revenue:

Cash discounts and distributor fees: We provide customary discounts on XPOVIO sales to our customers for prompt payment, the terms of which are explicitly stated in our contracts with such customers. We also pay fees to our customers for sales order management, data, and distribution services, the terms of which are also explicitly stated in our contracts with such customers. Such fees are not for a distinct good or service and, accordingly, are recorded as a reduction of revenue, as well as a reduction to accounts receivable (cash discounts) or as a component of accrued expenses (distributor fees).

Product returns: Consistent with industry practice, we offer our customers and other indirect purchasers a limited right of return for purchased units of XPOVIO for damage, defect, recall, and/or product expiry (beginning three months prior to the product's expiration date and ending six to twelve months after the product's expiration date). We estimate the amount of product sales that will be returned using quantitative and qualitative considerations, such as visibility into the inventory remaining in the distribution channel and historical returns data. Reserves for estimated returns are recorded as a reduction of revenue in the period that the related revenue is recognized, as well as a component of accrued expenses. We update our estimated return liability each reporting period based on actual shipments of XPOVIO subject to contractual return rights, changes in expectations about the amount of estimated and/or actual returns, and other qualitative considerations.

Chargebacks: Chargebacks for fees and discounts represent the estimated obligations resulting from our contractual commitments to provide products to qualified healthcare entities at prices lower than the list prices charged to our customers who purchase XPOVIO directly from us. Our customers charge us for the discount provided to the healthcare entities. Chargebacks are generally determined at the time of resale to the qualified healthcare provider by our customers. Accordingly, reserves for chargebacks consist of credits that we expect to issue for units that remain in the distribution channel inventory at the end of the reporting period that we expect will be sold to qualified healthcare entities, as well as chargebacks that customers have claimed, but for which we have not yet issued a credit. We record reserves for chargebacks based on contractual terms in the same period that the related revenue is recognized, resulting in a reduction of product revenue and accounts receivable. We generally issue credits to the customer for such amounts within a few weeks after the customer notifies us of the resale to a discount-eligible healthcare entity.

Government rebates: We are subject to discount obligations under state Medicaid programs, Medicare, the Department of Veterans Affairs, the Department of Defense, and others. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability, which is included as a component of accrued expenses. For Medicare, we estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under Medicare Part D. Our liability for these rebates consists of invoices received for claims from prior and current quarters that have not been paid or for which an invoice has not yet been received, estimates of claims for the current quarter, and estimated future claims that will be made for product that has been recognized as revenue, but which remains in distribution channel inventories at the end of the reporting period.

Other incentives: Other incentives offered by us include co-payment assistance, which we provide as financial assistance to patients with commercial insurance that requires prescription drug co-payments by the patient. We calculate the accrual for co-payment assistance based on estimates of claims and the average co-payment assistance amounts per claim that we expect to receive associated with sales of XPOVIO that have been recognized as revenue but remain in distribution channel inventories at the end of the reporting period. Such estimates are based on industry experience with similar products, as well as actual amounts from our product sales to date. Any adjustments to such estimated liabilities on units in the distribution channel at period end, as well as actual amounts incurred on units sold through the distribution channel during the period, are recorded in the same period that the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability, which is included as a component of accrued expenses.

Product revenue reserves and allowances: As noted above, cash discounts and chargebacks are recorded as reductions of accounts receivable and product returns, distributor fees, government rebates, and other incentives are recorded as a component of accrued expenses. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we will adjust these estimates, which would affect product revenue, net and earnings in the period in which such variances become known.

License Agreements

We generate revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain of our products and product candidates. Such agreements may include the transfer of intellectual property rights in the form of licenses, transfer of technological know-how, delivery of drug substances, research and development services, and participation on certain committees with the counterparty. Payments made by the customer may include non-refundable upfront

fees, payments upon the exercise of options, payments based upon the achievement of defined milestones, and royalties on sales of products and product candidates if they are approved and commercialized. Our license agreements are detailed in Note 5, "*License Agreements*".

At contract inception, we evaluate all goods or services in the agreement to determine if they are distinct. If they are not distinct, they are combined with other promised goods or services to create a bundle of promised goods or services that are distinct. Distinct goods or services and distinct bundles of goods or services are considered performance obligations. Optional future services where any additional consideration paid to us reflects their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations. Optional future services that are priced in a manner which provides the customer with a significant or incremental discount are considered performance obligations because they provide the customer with a material right.

We utilize judgment to estimate the transaction price at contract inception. We evaluate contingent milestones to determine if they should be included in the transaction price using the most likely amount method. Milestone payments that are not within our control, such as regulatory approvals, are not considered likely of being achieved until those approvals are received and are excluded from the transaction price using the most likely amount method. The transaction price is then allocated to each performance obligation on a relative standalone selling price basis, for which we recognize revenue as or when the performance obligations are satisfied. At the end of each reporting period, we re-evaluate our estimate of the transaction price, including the probability of achieving milestone payments that may not be subject to a material reversal, and adjust the transaction price if necessary. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license and other revenue in the period of adjustment.

We then determine whether the performance obligations are satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. We evaluate the measure of progress, as applicable, for each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded within deferred revenue. Contract liabilities within deferred revenue are recognized as revenue after control of the goods or services is transferred to the customer and all revenue recognition criteria have been met.

For arrangements that include a license of intellectual property and sales-based royalties, including sales-based milestone payments, we recognize revenue when the related sales occur because the license of intellectual property is deemed to be the predominant item to which the royalties relate.

Research and Development Expenses

Research and development costs are charged to expense as incurred and include, but are not limited to:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with CROs, CMOs and consultants that help conduct clinical trials and preclinical studies;
- the cost of acquiring, developing and manufacturing clinical trial materials, including comparator products;
- facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other supplies; and
- costs associated with preclinical activities and regulatory operations.

Costs for certain research and development activities, such as clinical trials, are recognized based on various inputs, including an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, and other information provided to us by our vendors based on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are accordingly reflected in our financial statements as prepaid or accrued research and development costs.

Selling, General and Administrative Expenses

Selling, general and administrative costs are charged to expense as incurred and consist primarily of salaries, benefits, travel, and other related costs, including stock-based compensation, for personnel in executive, finance, commercial and administrative functions. Other significant costs include facility costs not otherwise included in research and development expenses, legal fees relating to patent and corporate matters and fees for accounting and consulting services.

Accounting for Stock-Based Compensation

We grant stock-based awards to employees and non-employees, including stock options, restricted stock units ("RSUs"), performance-based restricted stock units ("PSUs") and shares issued under our employee stock purchase plan ("ESPP"). We account for all stock-based awards at their fair value as of the grant date and recognize compensation expense on the consolidated statements of operations on a straight-line basis over the vesting period of the award. We use the Black-Scholes option pricing model to determine the fair value of stock options as of the grant date. The fair value of RSUs is the quoted closing market price per share of our common stock on the Nasdaq Global Select Market on the grant date. Forfeitures are recognized as they occur.

PSUs are awards which will vest if certain performance goals are achieved over a certain performance period. Certain portions of certain PSU awards vest based on continuous service to the Company throughout the performance period even if the performance goal is not achieved. Stock-based compensation expense for PSUs is determined using the grant date fair value, which is the quoted closing market price per share of our common stock on the Nasdaq Global Select Market on the grant date. The grant date fair value of PSUs with a market condition also includes a discount that represents the likelihood that the related performance goals will not be achieved. Stock-based compensation expense for PSUs with a market condition is recognized on a straight-line basis over the service period. Market conditions include goals related to the performance of our common stock. Stock-based compensation expense for PSUs without a market condition is not recognized until the achievement of the performance goal is deemed probable (the "Probable Date"). At the Probable Date, we record a cumulative catch-up expense for the portion of the grant date fair value attributable to the period from the grant date to the Probable Date. The remaining expense is recognized over the remaining service period on a straight-line basis.

Foreign Currency Transactions

The functional currency of our subsidiaries in Germany and Israel are the Euro and Shekel, respectively. Foreign currency transaction gains and losses are recorded on the consolidated statements of operations and were immaterial for the years ended December 31, 2024, 2023 and 2022.

Income Taxes

We use the liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and the tax reporting basis of assets and liabilities and are measured using the enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. We provide a valuation allowance against deferred tax assets unless, based upon the available evidence, it is more likely than not that the deferred tax assets will be realized. We have evaluated available evidence and concluded that we may not realize the benefit of our deferred tax assets; therefore, a valuation allowance has been established for the full amount of the net deferred tax assets. We recognize interest and/or penalties related to income tax matters in income tax expense. Our state tax provision pertains to income generated by our KSC entity. Our foreign tax provision pertains to foreign income taxes due by our German and Israel subsidiaries, both of which operate on a cost-plus profit margin basis.

Net Loss Per Share

Basic net loss per common share is calculated using the two-class method by dividing the net loss allocated to common shares by the weighted-average number of common shares outstanding for the period. Diluted net loss per common share is calculated by adjusting net loss to remove the effects from potential dilutive common shares and dividing this adjusted amount by the weighted average number of common shares and potential dilutive common shares outstanding for the period. Potential dilutive common shares are not included if their effect is anti-dilutive.

As discussed further in Note 10, "*Long-Term Obligations*", we have the option to settle the conversion obligation for our 3.00% unsecured convertible senior notes due 2025 (the "2025 Notes") in cash, shares or any combination of the two. There was no impact of the 2025 Notes on the calculation of dilutive loss per common share during the years ended December 31, 2023 and 2022 because they were anti-dilutive in these periods. The table below describes the impact of the 2025 Notes on the calculation of dilutive loss per common share during the year ended December 31, 2024.

As discussed further in Note 10, "*Long-Term Obligations*", we have the option to settle the conversion obligation for our 6.00% secured convertible senior notes due 2029 (the "2029 Notes") in cash, shares or any combination of the two. The 2029 Notes were issued in May 2024 and did not impact the calculation of dilutive loss per common share during the year ended December 31, 2024 because they were anti-dilutive in this period.

As discussed further in Note 11, "*Common Share Warrants*", warrants to purchase up to 55,563,775 shares of our common stock were outstanding as of December 31, 2024. These warrants are not included in the calculation of basic net loss per share because the warrant holders do not have an obligation to share in our losses. There was no impact of these warrants on the calculation of dilutive loss per common share during the years ended December 31, 2024, 2023 and 2022 because they were anti-dilutive in these periods.

The following is a reconciliation of the numerator and denominator used to calculate diluted net loss per common share for the year ended December 31, 2024 (in thousands except per share amounts):

	For the Year Ended December 31, 2024
Net loss	$ (76,422)
Add back interest expense on the 2025 Notes	2,736
Add back gain on extinguishment of debt	(44,702)
Numerator for diluted net loss per common share (A)	$ (118,388)
Weighted-average number of common shares outstanding	121,863
Dilutive effect of 2025 Notes calculated using the if-converted method	4,946
Denominator for diluted net loss per common share (B)	126,809
Diluted net loss per common share (= A / B)	$ (0.93)

The following potentially dilutive securities were excluded from the calculation of diluted net loss per share due to their anti-dilutive effect under the treasury method (in thousands):

	As of December 31,		
	2024	2023	2022
Outstanding common share warrants	55,564	9,788	9,538
Outstanding stock options	6,383	8,621	13,026
Unvested RSUs and PSUs	12,768	7,666	3,403

Comprehensive Loss

Comprehensive loss consists of net loss and certain changes in stockholders' deficit that are excluded from net loss, which currently consists of unrealized gains and losses on investments and foreign currency translation adjustments.

3. Product Revenue

To date, our only source of product revenue has been from the U.S. sales of XPOVIO. The following table summarizes activity in each of the product revenue allowance and reserve categories (in thousands):

	Discounts and Chargebacks	Fees, Rebates, and Other Incentives	Returns	Total
Beginning balance as of January 1, 2022	$ 1,911	$ 2,306	$ 344	$ 4,561
Provision related to sales in the current year	17,920	9,979	219	28,118
Credits or payments made	(16,966)	(8,551)	(21)	(25,538)
Ending balance as of December 31, 2022	2,865	3,734	542	7,141
Provision related to sales in the current year	21,106	11,025	—	32,131
Credits or payments made	(21,455)	(10,089)	(224)	(31,768)
Ending balance as of December 31, 2023	2,516	4,670	318	7,504
Provision related to sales in the current year	29,346	18,021	3,172	50,539
Credits or payments made	(27,632)	(8,848)	(1,635)	(38,115)
Ending balance as of December 31, 2024	$ 4,230	$ 13,843	$ 1,855	$ 19,928

Discounts and chargebacks are recorded as reductions of accounts receivable, and returns, fees, rebates, and other incentives are recorded as a component of accrued expenses and other liabilities.

As of December 31, 2024 and 2023, net product revenue of $27.8 million and $17.8 million, respectively, was included in accounts receivable, net.

4. Inventory

Prior to regulatory approval, we expense costs relating to the production of inventory as research and development expenses in the period incurred. We capitalize the costs incurred to manufacture our products after regulatory approval when, based on our judgment, future commercialization is considered probable and the future economic benefit is expected to be realized. We value our inventories at the lower of cost or estimated net realizable value. We determine the cost of our inventories, which includes amounts related to materials and manufacturing overhead, on a first-in, first-out basis. Raw materials and work in process includes all inventory costs prior to packaging and labelling, including raw materials, active pharmaceutical ingredient, and drug product. Finished goods include packaged and labelled products.

Raw materials and work in process that may be used for either research and development or commercial sale are classified as inventory until the material is consumed or otherwise allocated for research and development. If the material is intended to be used for research and development, it is expensed as research and development once that determination is made.

We assess the recoverability of our inventory each reporting period and write-down any inventory that has become obsolete, that has a cost basis in excess of its estimated realizable value, or that is not expected to be sold or otherwise consumed before expiry. Inventory write-downs are recorded as cost of sales in the period the impairment is identified.

Cost of sales includes the cost of producing and distributing inventories related to sales of XPOVIO in the U.S. and sales of selinexor to our partners who commercialize our products outside of the U.S. Cost of sales is recognized in the period the related sales occur and includes compensation expense for employees involved with production and distribution, freight, and indirect overhead costs, as well as third-party royalties payable on net product revenue. Cost of sales may also include excess or obsolete inventory adjustment charges, abnormal costs, unabsorbed manufacturing and overhead costs, and manufacturing variances.

The following table presents our inventory (in thousands), all of which was related to XPOVIO:

	As of December 31, 2024	2023
Raw materials	$ 720	$ 553
Work in process	3,542	1,732
Finished goods	477	758
Total inventory	$ 4,739	$ 3,043

5. License Agreements

The following license agreements affected the consolidated financial statements during the years ended December 31, 2024, 2023 and 2022:

Antengene License Agreement

In May 2020, we entered into an amendment to our May 2018 license agreement (the "Original Antengene Agreement" and, as amended, the "Amended Antengene Agreement") with Antengene Therapeutics Limited, a corporation organized and existing under the laws of Hong Kong ("Antengene") and a subsidiary of Antengene Corporation Co. Ltd., a corporation organized and existing under the laws of the People's Republic of China, pursuant to which we expanded the territory licensed to Antengene in the Original Antengene Agreement for the exclusive development and commercialization rights of selinexor, eltanexor and KPT-9274, each for the diagnosis, treatment and/or prevention of all human oncology indications, as well as verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications ("Antengene Licensed Compounds").

Under the terms of the Amended Antengene Agreement, Antengene has the exclusive development and commercialization rights for the Antengene Licensed Compounds in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam, Australia and New Zealand (the "Antengene Territory"). Under the terms of the Original Antengene Agreement, we received an upfront cash payment of $11.7 million in 2018 and in June 2020 we received a one-time upfront cash payment of $11.7 million in connection with the Amended Antengene Agreement. We are also entitled to future milestone payments from Antengene if certain development, regulatory and commercialization goals are achieved. Finally, we are also eligible to receive tiered double-digit royalties based on future net sales of selinexor and eltanexor, and tiered single- to double-digit royalties based on future net sales of verdinexor and KPT-9274 in the Antengene Territory. In addition, upon completion of the manufacturing technology transfer plan, we will grant to Antengene non-exclusive rights to manufacture the Antengene Licensed Compounds solely for their development and commercialization in the Antengene Territory.

As part of the Amended Antengene Agreement, Antengene also has the right to participate in global clinical studies of the Antengene Licensed Compounds and will bear the cost and expense for patients enrolled in such global clinical studies in the Antengene Territory. Antengene is responsible for seeking regulatory and marketing approvals for the Antengene Licensed Compounds in the Antengene Territory, as well as any development of the products necessary to obtain such approvals. Antengene is also responsible for the commercialization of the Antengene Licensed Compounds in the Antengene Territory at its own cost and expense. Until Antengene manufactures its own drug supply, we will furnish clinical and commercial supplies to Antengene pursuant to supply agreements between us and Antengene, the costs of which will be borne by Antengene.

The Amended Antengene Agreement will continue in effect on a product-by-product, country-by-country basis until the later of the tenth anniversary of the first commercial sale of the applicable product in such country or the expiration of specified patent protection and regulatory exclusivity periods for the applicable product in such country. However, the Amended Antengene Agreement may be terminated earlier by (i) either party for breach of the Amended Antengene Agreement by the other party or in the event of the insolvency or bankruptcy of the other party, (ii) Antengene on a product-by-product basis for certain safety reasons or on a product-by-product, country-by-country basis for any reason with 180 days prior notice or (iii) us in the event Antengene challenges or assists with a challenge to certain of our patent rights.

We identified the following performance obligations in the Amended Antengene Agreement: exclusive licenses, initial data transfers, and a stand-ready obligation to provide initial clinical supply for each of the Antengene Licensed Compounds. We also identified as performance obligations the following customer options for each of the Antengene Licensed Compounds that were offered at a significant and incremental discount and represent material rights: (i) the material right for additional data transfers; (ii) the material right for additional clinical supply and related substance supply; (iii) the material right for manufacturing technology transfers and licenses; and (iv) the material right for the option for a backup compound, which represents Antengene's option to select a replacement compound in the event it elects to discontinue the development of the Antengene Licensed Compounds. All of the performance obligations that received an allocation of the initial transaction price of $11.7 million were fully satisfied as of December 31, 2021.

All development and regulatory milestones, which represent variable consideration, will be evaluated each reporting period and included in the transaction price if the milestone is considered likely of achievement and if it is probable that a significant revenue reversal will not occur in future periods. Milestones included in the transaction price will be fully recognized in revenue in the same reporting period because all performance obligations that received an allocation of the transaction price were fully satisfied as December 31, 2021.

Any consideration related to sales-based milestones, as well as royalties on net sales upon commercialization of XPOVIO by Antengene, are recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property licenses granted to Antengene.

Menarini License Agreement

In December 2021, we entered into a license agreement (the "Original Menarini Agreement") with Berlin-Chemie AG, an affiliate of the Menarini Group ("Menarini"), pursuant to which we granted Menarini a non-exclusive license to develop, and an exclusive license to commercialize, products containing selinexor (the "Product"), for all human oncology indications in the European Economic Area, United Kingdom, Switzerland, Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Uzbekistan, Ukraine, Turkey, Mexico, all Central America countries and all South America countries (collectively, the "Menarini Territory"). In March 2023, the Original Menarini Agreement was amended (the "Amended Menarini Agreement") to expand the Menarini Territory to include all countries in the continent of Africa and Saudi Arabia, United Arab Emirates, Kuwait, Oman, Qatar, Bahrain, Lebanon, Jordan, Iraq, and Yemen (together with the Menarini Territory, the "Expanded Menarini Territory"). In addition, we granted to Menarini a non-exclusive license to package and label the Product in or outside of the Expanded Menarini Territory for all human oncology indications solely to enable Menarini to commercialize the Product within the Expanded Menarini Territory.

Under the terms of the Amended Menarini Agreement, we will use commercially reasonable efforts to develop the Product, transfer any marketing approval or authorization with respect to the Product in the Expanded Menarini Territory to Menarini and to complete any post-marketing approval or authorization studies required by a regulatory authority as a condition of maintaining the approval in any country in the Expanded Menarini Territory. Menarini is obligated to use commercially reasonable efforts to apply for and obtain marketing approval or authorization of the Product, and to obtain price or reimbursement approval for the Product after approval of the relevant marketing approval or authorization, in each country of the Expanded Menarini Territory in each indication for which we have conducted a registrational clinical trial. Menarini is also obligated to use commercially reasonable efforts at its sole cost and expense to launch and commercialize the Product in each country of the Expanded Menarini Territory in each indication for which we have conducted a registrational clinical trial.

We received an upfront cash payment of $75.0 million in December 2021 under the Original Menarini Agreement and $3.5 million in April 2023 upon execution of the Amended Menarini Agreement. In addition, we are entitled to receive additional milestone payments from Menarini if certain development and sales performance milestones are achieved. We are further eligible to receive tiered royalties ranging from the mid-teens to mid-twenties based on future net sales of the Product in the Expanded Menarini Territory. The payments owed by Menarini to us are subject to reduction in specified circumstances. Menarini will reimburse us for 25% of all expenses we incur for the development of the Product during 2022 through 2025, provided that such reimbursements shall not exceed $15.0 million per calendar year. These amounts represent variable consideration and will be recognized as earned.

The Amended Menarini Agreement will continue in effect on a country-by-country basis until the last to occur among: (i) the fifteenth anniversary of the first commercial sale of the Product in the applicable country, (ii) the expiration of the last-to-expire of the licensed patent rights in the applicable country or (iii) the expiration of any regulatory exclusivity protection covering the Product in such country. However, the Amended Menarini Agreement may be terminated earlier by either party for (i) an uncured material breach of the Amended Menarini Agreement by the other party (A) on a country-by-country basis with respect to the country to which the breach does not affect the Amended Menarini Agreement as a whole or (B) in its entirety if the breach affects the Amended Menarini Agreement as a whole, or (ii) in the event of the insolvency or bankruptcy of the other party. We may also terminate the Amended Menarini Agreement for certain patent challenges by Menarini.

We assessed this arrangement and concluded that the contract counterparty, Menarini, is a customer. We identified the following material promises in the arrangement: the granting of a non-exclusive license to develop, and an exclusive license to commercialize the Product, as well as the initial transfer of know-how and information to Menarini. The Amended Menarini Agreement provides that we will supply to Menarini, and Menarini will purchase from us, all required quantities of Product for the Expanded Menarini Territory in accordance with a supply agreement separately entered into by and between us and Menarini in 2022 (the "Supply Agreement"). We determined that the promise of the Supply Agreement was not a performance obligation at the outset of the arrangement as the rate charged for the Product was not at a significant and incremental discount and therefore did not represent a material right. We then determined that the granting of the license and the initial transfer of know-how were not distinct from one another and must be combined as a performance obligation (the "Combined Performance Obligation"). Based on these determinations, we identified one distinct performance obligation at the inception of the contract: the Combined Performance Obligation. We further determined that the up-front payment of $75.0 million constituted the entirety of the consideration included in the transaction price at contract inception, which was allocated to the Combined Performance Obligation. The Combined Performance Obligation was fully satisfied as of December 31, 2021.

All development and regulatory milestones, which represent variable consideration, will be evaluated each reporting period and included in the transaction price if the milestone is considered likely of achievement and if it is probable that a significant revenue reversal will not occur in future periods. Milestones included in the transaction price will be fully recognized in revenue in the same reporting period because the Combined Performance Obligation was fully satisfied as of December 31, 2021.

Any consideration related to sales-based milestones, as well as royalties on net sales upon commercialization by Menarini, are recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property licenses granted to Menarini.

Summary of License and Other Revenue

The following table presents information about our license and other revenue (in thousands):

	For the Years Ended December 31,		
	2024	2023	2022
Menarini	$ 28,014	$ 24,360	$ 15,672
Antengene	1,680	2,713	13,353
Other	2,737	6,949	7,604
Total license and other revenue	$ 32,431	$ 34,022	$ 36,629

During the year ended December 31, 2024, we recognized (i) $15.0 million of revenue for the reimbursement of development-related expenses, $10.0 million of milestone revenue, $2.2 million of royalty revenue, and $0.8 million of other reimbursement revenue from Menarini; (ii) $1.7 million of royalty revenue from Antengene; and (iii) $2.0 million of milestone-related revenue, $0.4 million of royalty revenue, and $0.3 million of other reimbursement revenue from our other partners.

During the year ended December 31, 2023, we recognized (i) $15.0 million of revenue for the reimbursement of development related expenses, $4.0 million of milestone-related revenue, $3.5 million of license-related revenue, $1.1 million of royalty revenue, and $0.8 million of other reimbursement revenue from Menarini; (ii) $1.5 million of royalty revenue, and $1.2 million of other reimbursement revenue from Antengene; and (iii) $3.4 million of license-related revenue, $2.5 million of milestone-related revenue, $0.5 million of royalty revenue, and $0.5 million of other reimbursement revenue from our other partners.

During the year ended December 31, 2022, we recognized (i) $15.0 million of revenue for the reimbursement of development related expenses, $0.3 million of royalty revenue, and $0.4 million of other reimbursement revenue from Menarini; (ii) $7.8 million of milestone-related revenue, $3.8 million of royalty revenue, and $1.8 million of other reimbursement revenue from Antengene; and (iii) $5.2 million of royalty revenue and $2.3 million of milestone-related revenue from our other partners.

License and other revenue of $2.9 million and $9.1 million were included in accounts receivable, net as of December 31, 2024 and 2023, respectively. No license and other revenue was included in other current assets as of December 31, 2024. License and other revenue of $1.0 million was included in other current assets as of December 31, 2023.

6. Fair Value Measurements

Financial instruments, including cash, cash equivalents, accounts receivable, net, other current assets, other assets, restricted cash, accounts payable, and accrued expenses, are presented at amounts that approximate fair value as of December 31, 2024 and 2023.

Items classified as Level 2 consist of corporate debt securities, commercial paper, and U.S. government and agency securities. We estimate the fair values of these marketable securities by taking into consideration valuations obtained from third-party pricing sources. These pricing sources utilize industry standard valuation models, including both income and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include market pricing based on real-time trade data for the same or similar securities, issuer credit spreads, benchmark yields, and other observable inputs. We validate the prices provided by our third-party pricing sources by understanding the models used, obtaining market values from other pricing sources and analyzing pricing data in certain instances.

The following tables present information about our financial assets that have been measured at fair value and indicate the fair value hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

	As of December 31, 2024	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Money market funds	$ 46,990	$ 46,990	$ —	$ —
Commercial paper	5,072	—	5,072	—
Investments:				
Corporate debt securities	39,091	—	39,091	—
Commercial paper	3,166	—	3,166	—
U.S. government and agency securities	3,979	—	3,979	—
	$ 98,298	$ 46,990	$ 51,308	$ —

	As of December 31, 2023	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Money market funds	$ 27,963	$ 27,963	$ —	$ —
U.S. government and agency securities	1,998	—	1,998	—
Investments:				
Corporate debt securities	77,961	—	77,961	—
Commercial paper	13,744	—	13,744	—
U.S. government and agency securities	47,507	—	47,507	—
	$ 169,173	$ 27,963	$ 141,210	$ —

In certain cases where there is limited activity or less transparency around inputs to valuation, the related assets or liabilities are classified as Level 3. The following liabilities are measured at fair value at the end of each reporting period, with changes in fair value recognized as a component of other income (expense), net on our consolidated statements of operations. See Note 10, "*Long-Term Obligations*", to our consolidated financial statements for further discussion of the following Level 3 liabilities:

(1) The embedded derivative liability (the "HCRx Derivative") associated with a Revenue Interest Financing Agreement (the "Revenue Interest Agreement") we entered into with HCRx in September 2019 and as amended in June 2021, August 2023 and May 2024 (as amended, the "Amended Revenue Interest Agreement") is included as a component of the deferred royalty obligation on our consolidated balance sheets. The valuation method for the HCRx Derivative incorporates certain unobservable Level 3 key inputs including: (i) the probability-weighted net sales of XPOVIO and any of our other future products, including worldwide net product sales, upfront payments, milestones and royalties; (ii) our risk-adjusted discount rate; and (iii) the probability of a change in control occurring during the term of the instrument. The HCRx Derivative was deemed to have a de-minimus value as of December 31, 2024 primarily due to a $56.2 million decrease in the deferred royalty obligation during the year ended December 31, 2024.

(2) The embedded derivative liabilities (the "2029 Notes Derivatives") associated with the 2029 Notes are included as a component of the 2029 Notes on our consolidated balance sheets. The valuation method for the 2029 Notes Derivatives incorporates certain unobservable Level 3 key inputs including: (i) the volatility of our common stock price and (ii) our estimated credit spread.

(3) The warrants to purchase up to 45.8 million shares of our common stock issued in May 2024 (the "May 2024 Warrants") are classified as a long-term liability on our consolidated balance sheets. The valuation method for the May 2024 Warrants incorporates certain unobservable Level 3 key inputs including: (i) the volatility of our common stock price and (ii) an estimate of when the May 2024 Warrants will be exercised based on an option pricing model.

The following table sets forth a summary of the changes in the estimated fair value of the liabilities described above, which are all classified as Level 3 (in thousands):

	HCRx Derivative	2029 Notes Derivatives	May 2024 Warrants
Balance as of December 31, 2022	$ 2,800	$ —	$ —
Balance as of December 31, 2023	$ 2,800	$ —	$ —
Initial recognition	—	28,877	23,284
Change in fair value	(2,800)	(15,189)	(10,702)
Balance as of December 31, 2024	$ —	$ 13,688	$ 12,582

See Note 10, "*Long-Term Obligations*", to our consolidated financial statements for further discussion on the fair value of our debt instruments.

7. Investments

The following tables summarize our investments in debt securities, classified as available-for-sale (in thousands):

	As of December 31, 2024			
	Amortized Cost	Total Unrealized Gains	Total Unrealized Losses	Aggregate Fair Value
Corporate debt securities	$ 39,027	$ 66	$ (2)	$ 39,091
Commercial paper	3,165	1	—	3,166
U.S. government and agency securities	3,978	1	—	3,979
Total	$ 46,170	$ 68	$ (2)	$ 46,236

	As of December 31, 2023			
	Amortized Cost	Total Unrealized Gains	Total Unrealized Losses	Aggregate Fair Value
Corporate debt securities	$ 78,004	$ 79	$ (122)	$ 77,961
Commercial paper	13,734	13	(3)	13,744
U.S. government and agency securities	47,543	4	(40)	47,507
Total	$ 139,281	$ 96	$ (165)	$ 139,212

As of December 31, 2024 and 2023, we held 5 and 41 debt securities, respectively, that were in an unrealized loss position. The unrealized losses as of December 31, 2024 and 2023 were attributable to changes in interest rates and do not represent credit losses. We do not intend to sell the investments before recovery of their amortized cost bases, which may be at maturity. All our investments mature within two years from December 31, 2024. The following tables summarize our debt securities in an unrealized loss position for which an allowance for credit losses has not been recorded, aggregated by major security type and length of time in a continuous unrealized loss position (in thousands):

	As of December 31, 2024					
	Less than 12 Months		12 Months or Longer		Total	
	Aggregate Related Fair Value	Unrealized Losses	Aggregate Related Fair Value	Unrealized Losses	Aggregate Related Fair Value	Unrealized Losses
Corporate debt securities	$ 4,456	$ (2)	$ —	$ —	$ 4,456	$ (2)
Commercial paper	1,175	—	—	—	1,175	—
Total	$ 5,631	$ (2)	$ —	$ —	$ 5,631	$ (2)

	As of December 31, 2023					
	Less than 12 Months		12 Months or Longer		Total	
	Aggregate Related Fair Value	Unrealized Losses	Aggregate Related Fair Value	Unrealized Losses	Aggregate Related Fair Value	Unrealized Losses
Corporate debt securities	$ 50,322	$ (112)	$ 4,279	$ (10)	$ 54,601	$ (122)
Commercial paper	6,952	(3)	—	—	6,952	(3)
U.S. government and agency securities	27,191	(37)	1,997	(3)	29,188	(40)
Total	$ 84,465	$ (152)	$ 6,276	$ (13)	$ 90,741	$ (165)

8. Stockholders' Equity

Authorized Common Shares

On May 24, 2023, our stockholders approved an amendment to our Restated Certificate of Incorporation, as amended, to increase the number of authorized shares of our common stock from 200,000,000 shares to 400,000,000 shares.

On January 30, 2025, our stockholders approved an amendment to our Restated Certificate of Incorporation, as amended, to increase the number of authorized shares of our capital stock from 405,000,000 to 805,000,000 and the number of authorized shares of our common stock from 400,000,000 shares to 800,000,000 shares. In addition, on January 30, 2025, our stockholders approved an amendment to our Restated Certificate of Incorporation, as amended, to effect a reverse stock split of our issued shares of common stock at a ratio within the range of not less than 1-for-5 and not greater than 1-for-15, and a proportionate reduction in the number of authorized shares of common stock, with the exact ratio within such range and the implementation and timing of such reverse stock split to be determined at the sole discretion of our Board of Directors, without further approval or authorization of our stockholders.

Private Placement Offering

On December 5, 2022, we entered into a securities purchase agreement with certain institutional investors pursuant to which we issued and sold, in a private placement offering of securities, an aggregate of 31,791,908 shares of common stock. We received aggregate net proceeds of approximately $154.7 million.

Open Market Sale Agreement

On February 17, 2023, we entered into an Open Market Sale Agreement (the "2023 Open Market Sale Agreement") with Jefferies LLC, as agent ("Jefferies"). Under the 2023 Open Market Sale Agreement, we may issue and sell shares of our common stock having an aggregate offering price of up to $100.0 million (the "Shares") from time to time through Jefferies (the "2023 Open Market Offering"). Upon entry into the 2023 Open Market Sale Agreement, we terminated our previous Open Market Sale Agreement with Jefferies, as agent, which we had entered into in August 2018 (the "2018 Open Market Sale Agreement"), pursuant to which we could issue and sell shares of our common stock having an aggregate offering price of up to $175.0 million (the "Open Market Shares").

Under the 2023 Open Market Sale Agreement, Jefferies may sell the Shares by methods deemed to be an "at the market offering" as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended (the "Securities Act"). We may sell the Shares in amounts and at times to be determined by us from time to time subject to the terms and conditions of the 2023 Open Market Sale Agreement, but we have no obligation to sell any of the Shares in the 2023 Open Market Offering.

We or Jefferies may suspend or terminate the offering of Shares upon notice to the other party and subject to other conditions. We have agreed to pay Jefferies commissions for its services in acting as agent in the sale of the Shares in the amount of up to 3.0% of gross proceeds from the sale of the Shares pursuant to the 2023 Open Market Sale Agreement. We have also agreed to provide Jefferies with customary indemnification and contribution rights.

During the year ended December 31, 2022, we sold an aggregate of 3,991,652 Open Market Shares under the 2018 Open Market Sale Agreement, for net proceeds of $35.1 million. We did not sell any Open Market Shares under the 2018 Open Market Sale Agreement nor any Shares under the 2023 Open Market Sale Agreement during the years ended December 31, 2024 and 2023. As of December 30, 2024, $100.0 million of Shares was available for issuance and sale under the 2023 Open Market Sale Agreement.

9. Stock-based Compensation

On May 19, 2022, our stockholders approved the 2022 Equity Incentive Plan (the "2022 Plan"), succeeding our 2013 Stock Incentive Plan (the "2013 Plan"), which has expired and under which no further grants may be made. The 2022 Plan provides for the grant of incentive stock options, non-statutory stock options, stock appreciation rights, restricted stock awards, RSU awards and other stock-based awards. On May 24, 2023 and May 29, 2024, our stockholders approved an amendment to the 2022 Plan to increase the number of shares of our common stock available for issuance under the 2022 Plan by 5,000,000 and 6,000,000 shares, respectively. As of December 31, 2024, there were 8,070,510 shares available for future grants under the 2022 Plan.

Under the terms of the 2022 Plan and the 2013 Plan, we granted stock options, RSUs, and PSUs to our employees, officers, directors, consultants and advisors. Stock options have a ten-year term and an exercise price equal to the fair market value of a share of our common stock on the grant date. Stock options and RSUs vest over a period of one to four years. PSUs will vest if certain performance goals are achieved over a certain performance period. Certain portions of certain PSU awards vest based on continuous service to the Company throughout the performance period even if the performance goal is not achieved.

During 2024, 2023, and 2022, we also granted stock options and RSUs through inducement grants outside of our stockholder approved equity compensation plans as permitted under the Nasdaq Stock Market listing rules to certain employees to induce them to accept employment with us (collectively, "Inducement Awards"). In February 2022, our Board approved the 2022 Inducement Stock Incentive Plan (the "2022 Inducement Plan") under which 850,000 shares of common stock were initially reserved for issuance for inducement awards to be granted to newly hired full-time employees. In 2022, 2023, and 2024, the Board increased the number of shares reserved for issuance under the 2022 Inducement Plan by 850,000, 1,200,000, and 1,000,000, respectively. We assessed the terms of these Inducement Awards and determined there was no possibility that we would have to settle these awards in cash and therefore, equity accounting was applied. As of December 31, 2024, there were 1,523,535 shares available for future grants under the 2022 Inducement Plan.

As of December 31, 2024, we had 28,745,131 shares reserved for issuance, which includes shares available for future grants and outstanding stock options, RSUs and PSUs under the 2013 Plan, 2022 Plan, and Inducement Awards (including the Inducement Awards granted under the 2022 Inducement Plan).

Stock-based Compensation Expense

Total stock-based compensation expense recognized was as follows (in thousands):

	For the Years Ended December 31,		
	2024	2023	2022
Cost of sales	$ 227	$ 370	$ 226
Research and development	4,841	6,529	14,351
Selling, general and administrative	13,358	14,810	20,822
Total	$ 18,426	$ 21,709	$ 35,399

The total stock-based compensation expense recognized by award type was as follows (in thousands):

	For the Years Ended December 31,		
	2024	2023	2022
Options	$ 4,807	$ 8,862	$ 21,513
RSUs	10,961	10,662	12,587
PSUs	1,197	1,222	—
ESPP	691	963	1,299
Other	770	—	—
Total	$ 18,426	$ 21,709	$ 35,399

We agreed with our financial advisor to settle our fee for services provided in connection with the May 2024 refinancing transactions described in Note 10, "*Long-Term Obligations*", through the private placement of 6,872,027 shares of our common stock, resulting in $6.9 million being capitalized to our consolidated balance sheet as a debt issuance cost and $0.8 million being expensed to selling, general and administrative expense as stock-based compensation expense on our consolidated statements of operations during the year ended December 31, 2024.

During the year ended December 31, 2022, we accelerated the vesting and extended the exercise date of certain stock-based awards granted to our former Chief Executive Officer and former Chief Scientific Officer in connection with their departure from the Company in May 2022. These modifications resulted in the recognition of incremental stock-based compensation expense of $7.4 million for the year ended December 31, 2022.

Stock Options

The following table summarizes stock option activity related to the 2013 Plan, 2022 Plan, and Inducement Awards (including the stock option Inducement Awards granted under the 2022 Inducement Plan):

	Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Options outstanding as of December 31, 2023	8,620,810	$ 10.79	5.3	$ —
Granted	515,902	$ 0.91		
Forfeited	(2,671,431)	$ 11.47		
Expired	(82,000)	$ 38.13		
Options outstanding as of December 31, 2024	6,383,281	$ 9.33	4.4	$ —
Options exercisable as of December 31, 2024	5,362,973	$ 10.31	3.6	$ —

There were no stock options exercised for the year ended December 31, 2024. The total intrinsic value of stock options exercised for the years ended December 31, 2023 and 2022 was less than $0.1 million and $0.3 million, respectively.

The fair value of each stock option granted is estimated on the date of grant using the Black-Scholes option-pricing model. The following table summarizes the assumptions used in calculating the fair value of the stock option awards:

	For the Years Ended December 31,		
	2024	2023	2022
Volatility	80%	80%	79%-81%
Expected term (in years)	5.5-6.1	5.5-5.9	5.5-6.1
Risk-free interest rate	4.43%-4.63%	3.75%-4.21%	1.69%-4.23%
Dividend	—%	—%	—%

We use the simplified method to calculate the expected term as our historical exercise data does not provide a reasonable basis upon which to estimate the expected term. The expected term is applied to the stock option grant group as a whole, as we do not expect substantially different exercise or post-vesting termination behavior among our employee population. Our expected stock price volatility assumption is based on the historical volatility of our publicly traded stock. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. We account for forfeitures as they occur.

Using the Black-Scholes option-pricing model, the weighted-average grant date fair values of options granted during the years ended December 31, 2024, 2023 and 2022 was $0.64, $1.54 and $5.83 per share, respectively.

As of December 31, 2024, there was $2.6 million of unrecognized compensation expense related to unvested stock option awards, which is expected to be recognized over a weighted-average period of 1.1 years.

Restricted Stock Units and Performance-Based Restricted Stock Units

The following is a summary of RSU and PSU activity for the 2013 Plan, 2022 Plan, and Inducement Awards (including RSU Inducement Awards granted under the 2022 Inducement Plan):

	Number of Shares Underlying RSUs and PSUs	Weighted -Average Grant Date Fair Value
Unvested as of December 31, 2023	7,666,426	$ 4.40
Granted	8,889,717	$ 1.42
Forfeited	(1,351,473)	$ 2.52
Vested	(2,436,865)	$ 5.04
Unvested as of December 31, 2024	12,767,805	$ 2.41

The total fair value of RSUs and PSUs that vested during the years ended December 31, 2024, 2023 and 2022 was $2.8 million, $2.9 million, and $8.3 million, respectively. As of December 31, 2024, there was $19.0 million of unrecognized compensation expense related to unvested RSUs and PSUs, which is expected to be recognized over a weighted-average period of 1.8 years.

Employee Stock Purchase Plan

We have an ESPP that permits eligible employees to enroll in six-month offering periods. Participants may purchase shares of our common stock, through payroll deductions, at a price equal to 85% of the fair market value of the common stock on the first or last day of the applicable offering period, whichever is lower. Purchase dates under the ESPP occur on or about May 1 and November 1 each year. In 2013, our stockholders approved an annual increase in the number of shares of common stock authorized for issuance pursuant to the ESPP to be added on the first day of each fiscal year, commencing on January 1, 2015 and ending on December 31, 2023, equal to the lesser of 484,848 shares of our common stock, 1% of the number of outstanding shares on such date, or an amount determined by the Board (the "Evergreen Provision"). On May 24, 2023, our stockholders approved an amendment and restatement of our ESPP (the "Amended & Restated ESPP"), which (i) eliminated the Evergreen Provision and (ii) increased the number of shares of common stock authorized for issuance under the ESPP by 1,500,000 shares. On May 29, 2024, our stockholders approved an amendment to the Amended & Restated ESPP to increase the number of shares of our common stock available for issuance under the Amended & Restated ESPP by 5,000,000 shares. As of December 31, 2024, 4,655,260 shares of our common stock remained available for issuance under the Amended & Restated ESPP.

During the years ended December 31, 2024, 2023 and 2022, $1.5 million, $1.1 million and $2.3 million, respectively, was withheld from employees, on an after-tax basis, in order to purchase 1,977,558, 638,182 and 508,391 shares of our common stock, respectively. As of December 31, 2024, there was $0.2 million of total unrecognized stock-based compensation expense related to the Amended & Restated ESPP. The expense is expected to be recognized over a period of four months.

The fair value of the option component of the shares purchased under the Amended & Restated ESPP was estimated using the Black-Scholes option-pricing model with the following weighted-average assumptions:

	For the Years Ended December 31,		
	2024	2023	2022
Volatility	77% - 80%	77% - 92%	68% - 131%
Expected term (in years)	0.4-0.5	0.5	0.5
Risk-free interest rate	4.42% - 5.51%	4.58% - 5.51%	0.06% - 4.58%
Dividend	—%	—%	—%

10. Long-Term Obligations

2025 Notes

In October 2018, we issued $172.5 million aggregate principal amount of the 2025 Notes in a private offering to qualified institutional buyers in reliance on Rule 144A under the Securities Act. In connection with the issuance of the 2025 Notes, we incurred $5.6 million of debt issuance costs, which was being amortized to interest expense using the effective interest method over seven years. In May 2024, we exchanged $148.0 million aggregate principal amount of our 2025 Notes for (i) $111.0 million aggregate principal amount of our 2029 Notes and (ii) the May 2024 Warrants to purchase up to 45.8 million shares of our common stock. The 2029 Notes and the May 2024 Warrants are described in more detail below. $24.5 million in aggregate principal amount of the 2025 Notes remained outstanding following completion of the May 2024 exchange transactions (the "Remaining 2025 Notes") and as of December 31, 2024.

The Remaining 2025 Notes are senior unsecured obligations and bear interest at a rate of 3.00% per year payable semiannually in arrears on April 15 and October 15 of each year. Upon conversion, the Remaining 2025 Notes will be converted into cash, shares of our common stock, or a combination of cash and shares of our common stock, at our election. The Remaining 2025 Notes are subject to redemption at our option, in whole or in part, if the conditions described below are satisfied. Holders may require us to repurchase their Remaining 2025 Notes following a fundamental change (as defined within the indenture governing the 2025 Notes) at a cash repurchase price generally equal to the principal amount of the Remaining 2025 Notes to be repurchased, plus accrued and unpaid interest. The Remaining 2025 Notes will mature on October 15, 2025, unless earlier converted, redeemed or repurchased in accordance with their terms. Subject to satisfaction of certain conditions and during the periods described below, the Remaining 2025 Notes may be converted at an initial conversion rate of 63.0731 shares of common stock per $1,000 principal amount of the Remaining 2025 Notes (equivalent to an initial conversion price of approximately $15.85 per share of common stock).

Holders of the Remaining 2025 Notes may convert all or any portion of their Remaining 2025 Notes, in multiples of $1,000 principal amount, at their option at any time prior to the close of business on the business day immediately preceding June 15, 2025 only under the following circumstances:

(1) during any calendar quarter, if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on, and including, the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price for the Remaining 2025 Notes on each applicable trading day;

(2) during the five-business day period immediately after any five consecutive trading day period (the "Measurement Period") in which the trading price per $1,000 principal amount of Remaining 2025 Notes for each trading day of the Measurement Period was less than 98% of the product of the last reported sale price of our common stock and the conversion rate on each such trading day;

(3) if we call the Remaining 2025 Notes for redemption, until the close of business on the business day immediately preceding the redemption date; or

(4) upon the occurrence of specified corporate events as described within the indenture governing the 2025 Notes.

As of December 31, 2024, none of the above circumstances had occurred and as such, the Remaining 2025 Notes could not have been converted.

We may redeem for cash all or part of the Remaining 2025 Notes at our option if the last reported sale price of our common stock equals or exceeds 130% of the conversion price then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period ending within five trading days prior to the date on which we send any notice of redemption. The redemption price will be 100% of the principal amount of the Remaining 2025 Notes to be redeemed, plus accrued and unpaid interest, if any. In addition, calling any convertible note for redemption will constitute a make-whole fundamental change with respect to that convertible note, in which case the conversion rate applicable to the conversion of that convertible note, if it is converted in connection with the redemption, will be increased in certain circumstances. We did not redeem any of the Remaining 2025 Notes as of December 31, 2024.

The outstanding balances of the 2025 Notes consisted of the following (in thousands):

	As of December 31,	
	2024	2023
Principal	$ 24,500	$ 172,500
Less: unamortized debt issuance costs	(74)	(1,581)
2025 Notes	$ 24,426	$ 170,919

We determined the expected life of the 2025 Notes was equal to its seven-year term and the effective interest rate was 3.53%. As of December 31, 2024, the "if-converted value" did not exceed the remaining principal amount of the 2025 Notes. The fair value of the 2025 Notes is influenced by market interest rates, our stock price and stock price volatility, and has been classified as Level 2 within the fair value hierarchy as it uses quoted prices in active markets. The estimated fair value of the 2025 Notes as of December 31, 2024 and 2023 was $19.1 million and $87.9 million, respectively.

The following table sets forth total interest expense recognized related to the 2025 Notes (in thousands):

	For the Years Ended December 31,		
	2024	2023	2022
Contractual interest expense	$ 2,354	$ 5,175	$ 5,175
Amortization of debt issuance costs	382	814	812
Total interest expense	$ 2,736	$ 5,989	$ 5,987

Future minimum payments on the Remaining 2025 Notes were as follows (in thousands):

Years ended December 31,	Future Minimum Payments
Minimum payments due in 2025	$ 25,236
Less: interest expense and unamortized debt issuance costs	(810)
2025 Notes	$ 24,426

Senior Secured Term Loan

On May 8, 2024, we entered into a credit and guaranty agreement (the "Credit Agreement") with certain existing holders of the 2025 Notes and HCRx, which provides for a senior secured term loan facility of $100.0 million (the "Term Loan"). The Term Loan matures in May 2028 and bears interest at a variable rate equal to the applicable secured overnight financing rate plus 9.25%, subject to a floor of 3.00%. Principal payments under the Term Loan will begin in June 2026, and consist of quarterly cash payments in the amount of 6.25% of the aggregate principal amount of the Term Loan, with the remaining principal due when the Term Loan matures in May 2028.

We can prepay the Term Loan at any time. All repayments, including prepayments, are subject to a redemption fee of 3.00% of the principal paid. Prepayments made before May 8, 2027 are subject to a prepayment premium ranging from 3.00% to 5.00% of the principal prepaid. The prepayment premium for prepayments made before May 8, 2025 also includes the unpaid interest that would have accrued on the amount being prepaid through May 8, 2025. In addition, we are required to repay the Term Loan with proceeds from certain asset sales and condemnation events, subject, in some cases, to reinvestment rights.

All obligations under the Credit Agreement are secured on a first priority basis, subject to certain exceptions, by substantially all of our assets. The Credit Agreement contains customary covenants, including a requirement to maintain cash, cash equivalents and investments of at least $25.0 million at all times, and restrictions on indebtedness, liens, investments, fundamental changes, asset sales, licensing transactions, dividends, modifications to material agreements, payment of subordinated indebtedness, and other matters customarily restricted in such agreements. Specifically, we are prohibited from exclusively licensing, selling or otherwise disposing of U.S. rights to oncology indications of selinexor. As of December 31, 2024, we were in compliance with these covenants. If certain events of default occur, the Term Loan may be due and payable immediately. These events include the withdrawal of approval of certain indications of selinexor, payment defaults, covenant defaults, bankruptcy, cross-defaults to certain other agreements, change in control and lien priority.

The outstanding balance of the Term Loan consisted of the following (in thousands):

	As of December 31, 2024
Principal	$ 100,000
Less: unamortized debt issuance costs	(5,397)
Term Loan	$ 94,603

We determined the expected life of the Term Loan was equal to its four-year term and the effective interest rate is approximately 17%. The principal value of the Term Loan approximates its fair value due to the variable interest rate. In connection with the issuance of the Term Loan, we incurred $6.8 million of debt issuance costs, which are being amortized to interest expense using the effective interest method over four years. We recognized $10.8 million of interest expense related to the Term Loan during the year ended December 31, 2024, which consisted of $9.4 million of contractual interest expense and $1.4 million of debt issuance cost amortization.

Future minimum payments on the Term Loan as of December 31, 2024 were as follows (in thousands):

Years ended December 31,	Future Minimum Payments
2025	$ 13,854
2026	32,517
2027	35,707
2028	60,607
Total minimum payments	142,685
Less: interest expense and unamortized debt issuance costs	(48,082)
Term Loan	$ 94,603

2029 Notes

On May 13, 2024, pursuant to privately-negotiated agreements with certain holders of the 2025 Notes, we exchanged $148.0 million aggregate principal amount of 2025 Notes for (i) $111.0 million aggregate principal amount of the 2029 Notes and (ii) May 2024 Warrants to purchase up to 45.8 million shares of our common stock.

On May 13, 2024, we also issued $5.0 million aggregate principal amount of the 2029 Notes to HCRx in exchange for a $5.0 million reduction in our deferred royalty obligation. The 2029 Notes are second-lien secured obligations of the Company and bear interest at a rate of 6.00% per year payable quarterly in arrears beginning on June 30, 2024. The 2029 Notes will mature on May 13, 2029, unless earlier converted, redeemed or repurchased in accordance with their terms.

The 2029 Notes will be convertible into shares of our common stock at an initial conversion rate of 444.4444 shares per $1,000 principal amount (the "Conversion Option"), which is equivalent to a conversion price of $2.25 per share of common stock and subject to adjustment upon the occurrence of certain events and customary anti-dilution adjustments. Upon conversion of the 2029 Notes, we will deliver shares of our common stock plus cash in lieu of any fractional shares to the holders of the 2029 Notes. Holders of the 2029 Notes may convert their 2029 Notes at any time prior to the close of business on May 13, 2029.

On or after May 13, 2026, we may redeem for cash all or a portion of the 2029 Notes if the last reported sale price of our common stock equals or exceeds 130% of the conversion price then in effect for at least 20 trading days during any 30 consecutive trading day period (the "Redemption Option"). The redemption price will be equal to the principal amount of the 2029 Notes to be redeemed, plus any accrued and unpaid interest as of the redemption date. The redemption price will also include an amount equal to the aggregate value of all remaining interest payments on the 2029 Notes to be redeemed from the redemption date through maturity, which is payable in cash or, under certain circumstances and if we so elect, in shares of our common stock or a combination of cash and our common stock. Any shares of our common stock used to pay this amount will be valued based on their market price at the time of the redemption. In some cases, we will be required to make an offer to repurchase the 2029 Notes at a 101% premium with proceeds from certain asset sales, subject, in some cases, to reinvestment rights.

If certain corporate events occur prior to the maturity date, a holder that elects to convert their 2029 Notes may be entitled to receive a payment from us, in cash or, under certain circumstances and if we so elect, in shares of our common stock, or a combination of cash and our common stock, based on an increase in the conversion rate in connection with such corporate event. In addition, if we undergo certain fundamental changes, holders may require us to repurchase for cash all or any portion of their 2029 Notes at a price equal to the principal amount of the 2029 Notes to be repurchased, plus any accrued and unpaid interest as of the repurchase date.

No holder will be entitled to receive shares of our common stock in connection with the 2029 Notes if such receipt would cause the holder (together with its affiliates) to own more than 4.99% (subject to increase or decrease at the election of the holder, but in no event to exceed 19.99%) of the number of shares of the common stock outstanding immediately after giving effect to such event. In addition, a holder may elect to receive pre-funded warrants with respect to any shares of common stock that would otherwise be issuable in connection with the 2029 Notes but for the foregoing ownership limitations. These pre-funded warrants will have an exercise price of $0.0001 per share and will not expire. As of December 31, 2024, no pre-funded warrants have been issued.

All obligations under the 2029 Notes are secured on a second priority basis by the same collateral that secures the obligations under the Term Loan. The 2029 Notes contain covenants and events of default that are generally consistent with the Term Loan. As of December 31, 2024, we were in compliance with these covenants.

We accounted for the exchange of the 2025 Notes for the 2029 Notes and May 2024 Warrants as a debt extinguishment because the terms of the 2029 Notes are substantially different from the terms of the 2025 Notes. We recognized a $44.7 million gain on extinguishment of debt during the year ended December 31, 2024, the components of which are shown in the following table (in thousands):

Consolidated Balance Sheet Line	Transaction	Amount
Convertible senior notes due 2025	Extinguishment of 2025 Notes - principal	$ 148,000
Convertible senior notes due 2025	Extinguishment of 2025 Notes - debt issuance costs	(1,125)
Convertible senior notes due 2029	Issuance of 2029 Notes recorded at fair value	(78,889)
Common stock warrants	Issuance of May 2024 Warrants recorded at fair value	(23,284)
	Gain on extinguishment of debt	$ 44,702

As required by extinguishment accounting, the 2029 Notes received by the holders of the 2025 Notes were recorded at their initial fair value of $78.9 million as of May 8, 2024, which was estimated using a risk-neutral convertible bond model implemented using a binomial lattice which incorporates certain unobservable Level 3 key inputs including: (i) the volatility of our common stock price and (ii) our estimated credit spread. The $32.1 million difference between the initial fair value of $78.9 million and the principal amount of $111.0 million will be amortized to interest expense over the five-year term of the 2029 Notes using the effective interest method over five years.

In connection with the issuance of the 2029 Notes, we incurred $5.0 million of debt issuance costs, which are being amortized to interest expense using the effective interest method over five years.

We have determined that the Conversion Option and Redemption Option are embedded derivatives that require bifurcation from the debt instrument and fair value recognition. These derivatives are referred to as the 2029 Notes Derivatives in Note 6, "*Fair Value Measurements*", to our consolidated financial statements. The 2029 Notes Derivatives were bifurcated at their initial fair value of $28.9 million.

The following is a summary of the debt issuance costs and discounts being amortized to interest expense over the term of the 2029 Notes using the effective interest method, resulting in an effective interest rate of approximately 27% (in thousands):

	Amount
Initial fair value adjustment	$ 32,111
Debt issuance costs	4,981
Bifurcation of embedded derivatives	28,877
Debt issuance costs and discounts related to the 2029 Notes	$ 65,969

The outstanding balance of the 2029 Notes consisted of the following (in thousands):

	As of December 31, 2024
Principal	$ 116,000
Less: unamortized debt issuance costs and discounts	(61,343)
Plus: fair value of bifurcated derivative	13,688
2029 Notes	$ 68,345

We determined the expected life of the 2029 Notes was equal to its five-year term. As of December 31, 2024, the "if-converted value" did not exceed the remaining principal amount of the 2029 Notes. The fair value of the 2029 Notes is influenced by market

interest rates, our stock price and stock price volatility, and has been classified as Level 3 within the fair value hierarchy as it uses unobservable inputs. The estimated fair value of the 2029 Notes as of December 31, 2024 was approximately $81.7 million.

We recognized $9.0 million of interest expense related to the 2029 Notes during the year ended December 31, 2024, which consisted of $4.6 million of amortization and $4.4 million of contractual interest expense.

Future minimum payments on the 2029 Notes as of December 31, 2024 were as follows (in thousands):

Years ended December 31,	Future Minimum Payments
2025	$ 6,960
2026	6,960
2027	6,960
2028	6,960
2029	118,552
Total minimum payments	146,392
Less: interest expense and unamortized debt issuance costs and discounts	(91,735)
Plus: fair value of bifurcated derivative	13,688
2029 Notes	$ 68,345

Deferred Royalty Obligation

In September 2019, we entered into the Revenue Interest Agreement with HCRx, which was subsequently amended in June 2021, August 2023, and May 2024, under which we have received a total of $135.0 million, less certain transaction expenses. In exchange for this amount, HCRx receives payments from us at a percentage of net revenues of selinexor and any of our other future products, including worldwide net product sales and upfront payments, milestones, and royalties. Total payments to HCRx are capped at $263.3 million (the "Payment Cap").

In May 2024, we entered into an amendment (the "HCRx Amendment") to the Amended Revenue Interest Agreement with HCRx, pursuant to which we:

(1) made a cash payment to HCRx in the amount of $49.5 million;

(2) delivered to HCRx a Term Loan note with a principal amount of $15.0 million; and

(3) delivered to HCRx 2029 Notes with a principal amount of $5.0 million.

As the repayment of the funded amount is contingent upon worldwide net product sales and upfront payments, milestones, and royalties, the repayment term may be shortened or extended depending on actual worldwide net product sales and upfront payments, milestones, and royalties. The repayment period expires on the earlier of (i) the date in which HCRx has received cash payments totaling $263.3 million or (ii) the legal maturity date of October 1, 2031. If HCRx has not received total payments equal to $263.3 million by October 1, 2031, we will be required to pay an amount equal to $135.0 million plus a specific annual rate of return less payments previously paid to HCRx.

In the event of a change of control, an event of default, including, among others, our failure to pay any amounts due to HCRx, insolvency, our failure to pay indebtedness when due, the revocation of regulatory approval of XPOVIO in the U.S. or our breach of any covenant contained in the Amended Revenue Interest Agreement and our failure to cure the breach within the prescribed timeframe, we are obligated to pay HCRx an amount equal to $263.3 million less payments previously paid to HCRx.

After giving effect to the above, as of May 2024, we had made aggregate payments under the Amended Revenue Interest Agreement totaling $135.0 million and the maximum remaining amount we owed to HCRx was $128.3 million. After May 2024, we are obligated to make quarterly payments in the amount of a fixed percentage of our net product revenues, upfront payments, milestones, and royalties earned in the applicable quarter, subject to the provisions in the Amended Revenue Interest Agreement described earlier in this footnote.

The HCRx Amendment also subordinates the indebtedness and liens under the Amended Revenue Interest Agreement to the indebtedness and liens under the Term Loan, and, subject to certain exceptions, makes the indebtedness and liens under the Amended Revenue Interest Agreement pari passu with the indebtedness and liens under the 2029 Notes.

We have evaluated the terms of the Amended Revenue Interest Agreement and concluded that its features are similar to those of a debt instrument. Accordingly, we have accounted for the transaction as long-term debt and presented it as a deferred royalty obligation on our consolidated balance sheets.

We have also determined that the repayment of $263.3 million, less all payments made to date, upon a change of control is an embedded derivative that requires bifurcation from the debt instrument and fair value recognition as further described in Note 6, "*Fair Value Measurements*".

As of December 31, 2024, we have made $143.4 million in payments to HCRx. The effective interest rate as of December 31, 2024 was approximately 16%. We have incurred debt issuance costs totaling $1.7 million, which have been netted against the debt and are being amortized over the estimated term of the debt using the effective interest method, adjusted on a prospective basis for changes in the underlying assumptions and inputs.

The carrying value of the deferred royalty obligation as of December 31, 2024 and 2023 was $73.5 million and $129.7 million, respectively, which included the carrying amount of the debt, the fair value of the bifurcated embedded derivative liability, and unamortized debt issuance costs. The carrying value of the deferred royalty obligation approximated fair value as of December 31, 2024 and 2023 and was based on our estimates of future payments to HCRx over the life of the arrangement, which are considered Level 3 inputs.

11. Common Share Warrants

Equity Classified Common Share Warrants

On December 5, 2022, we issued to certain institutional investors, in a private placement offering of securities, warrants to purchase up to 9,537,563 shares of common stock at an exercise price of $6.36 per share. The warrants are exercisable through December 7, 2027. As of December 31, 2024, all of these warrants were outstanding.

On August 1, 2023, we issued warrants to HCRx to purchase up to 250,000 shares of common stock at an exercise price of $2.25 per share. In May 2024, the exercise price was reduced to $1.10 per share in connection with the HCRx Amendment. The warrants are exercisable through August 1, 2030. As of December 31, 2024, all of these warrants were outstanding.

Liability-Classified Common Share Warrants

In connection with the exchange of the 2025 Notes for the 2029 Notes described in further detail in Note 10, "*Long-Term Obligations*", we issued the May 2024 Warrants to certain 2025 Note holders to purchase up to 45,776,213 shares of our common stock at an exercise price of $1.10 per share, subject to customary antidilution adjustments. The May 2024 Warrants are exercisable through May 13, 2029. If the closing price of our common stock exceeds two times the then current exercise price of the warrants, which is currently equal to $2.20, for 20 trading days during any 30 consecutive trading day period, we can require the holder to exercise the May 2024 Warrants. As of December 31, 2024, the May 2024 Warrants to purchase 45,776,212 shares of our common stock were outstanding. Under the terms of the May 2024 Warrants, a holder cannot receive shares of our common stock if such receipt would cause the holder (together with its affiliates) to own more than 4.99% (subject to increase or decrease at the election of the holder, but in no event to exceed 19.99%) of our common stock outstanding on the date of receipt. In addition, a holder may elect to receive pre-funded warrants with respect to any common stock that would otherwise be issuable but for the foregoing ownership limitations. These pre-funded warrants will have an exercise price of $0.0001 per share and will not expire. As of December 31, 2024, no pre-funded warrants have been issued.

The May 2024 Warrants were classified as a long-term liability in our consolidated balance sheet because they did not meet the criteria for equity classification and are measured at fair value at the end of each reporting period as further described in Note 6, "*Fair Value Measurements*."

12. Commitments and Contingencies

Operating Leases

We determine if an arrangement contains a lease at contract inception based on the facts and circumstances in the arrangement. Lease classification, recognition, and measurement are then determined at the lease commencement date. For arrangements that contain a lease we (i) identify lease and non-lease components, (ii) determine the consideration in the contract, (iii) determine whether the lease is an operating or financing lease; and (iv) recognize lease right-of-use assets and liabilities. Lease liabilities and their

corresponding right-of-use assets are recorded based on the present value of lease payments over the expected lease term. We have elected not to separate lease components and non-lease components for leases of office or other space.

The interest rate implicit in lease contracts is typically not readily determinable and as such, we use our 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. In determining the incremental borrowing rate, we consider (i) our estimated public credit rating, (ii) our observable debt yields, as well as other bonds in the market issued by other companies with similar credit ratings as us, and (iii) adjustments necessary for collateral, lease term, and inflation or foreign currency.

Most leases include options to renew and/or terminate the lease, which can impact the lease term. The exercise of these options is at our discretion and we do not include any of these options within the expected lease term as we are not reasonably certain we will exercise these options. Leases that have a lease term of 12 months or less at commencement date are excluded from this treatment and are recognized on a straight-line basis over the term of the lease.

Fixed, or in substance fixed, lease payments on our operating lease are recognized over the expected term of the lease on a straight-line basis. Variable lease expenses that are not considered fixed, or in substance fixed, are recognized as incurred. Fixed and variable lease expense on our operating lease is recognized within operating expenses on our consolidated statements of operations.

We are party to an operating lease where we currently lease a total of 98,502 square feet of office and research space in Newton, Massachusetts. In November 2024, we amended this lease (as amended, the "Newton, MA Lease") which reduced the leased premises to 52,224 square feet of solely office space as of October 1, 2025 and extended the term of the Newton MA Lease for an additional five years, from October 1, 2025 to September 30, 2030. The lease contains a renewal option for an additional five years which was not included in the lease term as its exercise is not reasonably certain. Pursuant to the Newton, MA Lease, we have provided a security deposit in the form of a cash-collateralized letter of credit in the amount of $0.3 million, which is classified within long-term restricted cash on the consolidated balance sheets.

The Newton, MA Lease provides for increases in future minimum annual rental payments, as defined in the lease agreement. The operating lease expense for each of the years ended December 31, 2024, 2023 and 2022 was $2.8 million. Variable lease costs pertain to reimbursement of certain landlord expenses and were immaterial for each of the years ended December 31, 2024, 2023 and 2022.

In addition, we are party to certain short-term leases having a term of twelve months or less at the commencement date. We recognize short-term lease expense on a straight-line basis and do not record a related right-of use asset or lease liability for such leases. These costs were immaterial for the years ended December 31, 2024, 2023 and 2022.

We review the carrying values of our lease assets for possible impairment whenever events or changes in circumstances indicate that the carrying amounts of the assets may not be recoverable. We have not recorded an impairment in any period since inception.

Lease Commitments

As of December 31, 2024, future minimum lease payments under non-cancellable operating lease agreements for which we have recognized operating lease right-of-use assets and liabilities are as follows (in thousands):

Years ending December 31,	Future Minimum Payments
2025	$ 1,490
2026	1,880
2027	1,932
2028	1,985
2029	2,037
2030	1,557
Total minimum lease payments	10,881
Less: present value adjustment	(3,731)
Operating lease liabilities	$ 7,150

As of December 31, 2024, the remaining lease term on the Newton, MA Lease was 5.8 years and the discount rate used to calculate the operating lease liability was 14.5%.

Litigation

From time to time we may face legal claims or actions in the normal course of business. There are no outstanding legal claims or material actions as of December 31, 2024.

13. Accrued Expenses

Accrued expenses consisted of the following (in thousands):

	As of December 31,	
	2024	2023
Research and development costs	$ 26,711	$ 19,601
Compensation and employee-related costs	13,915	16,510
Interest	1,857	13,454
Product rebates, discounts, reserves, and royalties	13,397	4,706
Other	4,772	7,123
Total accrued expenses	$ 60,652	$ 61,394

14. Property and Equipment, Net

Property and equipment are recorded at cost, less accumulated depreciation and amortization. Depreciation and amortization expense is recorded using the straight-line method over the estimated useful lives of the respective assets, generally three to five years. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful economic lives of the related assets. Expenditures for maintenance and repairs are charged to expense while the costs of significant improvements are capitalized. Upon retirement or sale, the costs of the assets disposed of and the related accumulated depreciation or amortization is removed from the consolidated balance sheets and any related gains or losses are reflected on the consolidated statements of operations. Property and equipment, net consisted of the following (in thousands):

		As of December 31,	
	Estimated Useful Life (In Years)	2024	2023
Laboratory equipment	4	$ 972	$ 830
Furniture and fixtures	5	654	654
Office and computer equipment	3	587	809
Leasehold improvements	Lesser of useful life or lease term	4,878	4,878
Total property and equipment		7,091	7,171
Less accumulated depreciation and amortization		(6,691)	(6,565)
Total property and equipment, net		$ 400	$ 606

15. 401(k) Plan

We have a 401(k) retirement and profit-sharing plan (the "401(k) Plan") covering all qualified employees. The 401(k) Plan allows each participant to contribute a portion of their base wages up to an amount not to exceed an annual statutory maximum. Effective January 1, 2011, we adopted a Safe Harbor Plan that provides a Company match up to 4% of components of employee compensation. We contributed a match of $2.5 million, $3.7 million, and $3.1 million to the 401(k) Plan for the years ended December 31, 2024, 2023 and 2022, respectively.

16. Income Taxes

We recorded an income tax provision of $0.1 million, $0.3 million, and $0.4 million for the years ended December 31, 2024, 2023 and 2022, respectively. Our current income tax provision consists of state income tax due from our KSC entity through its dissolution in October 2024, as well as foreign income taxes due from our German and Israel subsidiaries, both of which operate on a cost-plus profit margin. We did not have a deferred income tax provision for the years ended December 31, 2024, 2023 and 2022.

The components of loss before income taxes were as follows (in thousands):

	For the Years Ended December 31,		
	2024	2023	2022
Foreign	$ 80	$ 247	$ 892
U.S.	(76,445)	(143,023)	(165,814)
Total	$ (76,365)	$ (142,776)	$ (164,922)

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of our deferred tax assets are comprised of the following (in thousands):

	As of December 31,	
	2024	2023
Deferred tax assets:		
U.S. and state net operating loss carryforwards	$ 189,335	$ 198,158
Research and development credits	117,607	108,682
Fixed assets and intangible assets	23,657	25,028
Stock-based compensation	5,365	8,500
Accruals and other temporary differences	8,592	6,380
Interest Expense - Sec 163(j)	7,234	6,894
Lease liability	1,752	1,461
Deferred royalty obligation	18,439	8,310
Capitalized research and development	64,919	47,986
Deferred royalty embedded derivative	6,437	671
Debt restructuring	3,522	—
Unicap - Sec 263A	1,227	800
Valuation allowance	(446,646)	(411,838)
Total deferred tax assets	1,440	1,032
Deferred tax liabilities:		
Convertible debt amortization	—	(7)
Right-of-use asset	(1,440)	(1,025)
Total deferred tax liabilities	(1,440)	(1,032)
Net deferred tax assets	$ —	$ —

The Tax Cuts and Jobs Act of 2017 ("TCJA") requires taxpayers to capitalize and amortize research and development expenditures, resulting in capitalized research and development costs of $120.7 million and $135.9 million as of December 31, 2024 and 2023, respectively. We will amortize these costs for tax purposes over five years for research and development performed in the U.S. and over 15 years for research and development performed outside the U.S.

On May 13, 2024, we exchanged $148.0 million aggregate principal amount of the 2025 Notes for (i) $111.0 million aggregate principal amount of the 2029 Notes and (ii) May 2024 Warrants to purchase up to 45.8 million shares of our common stock, as described in further detail in Note 10, "*Long-Term Obligations*". This created $93.2 million of taxable income related to the cancellation of debt, which was fully offset by our net operating loss carryforwards.

We have evaluated the positive and negative evidence bearing upon the realizability of our deferred tax assets. Based on our history of operating losses, we have concluded that it is more likely than not that the benefit of our deferred tax assets will not be realized. Accordingly, we have provided a full valuation allowance for deferred tax assets as of December 31, 2024 and 2023. The valuation allowance increased by approximately $34.8 million during the year ended December 31, 2024 primarily due to increased capitalization of research and development expenditures as required by changes to the tax laws from the TCJA as described above.

A reconciliation of income tax expense computed at the statutory federal income tax rate to income taxes as reflected in the financial statements is as follows:

	For the Years Ended December 31,		
	2024	2023	2022
Federal income tax expense at statutory rate	21.0%	21.0%	21.0%
State income tax, net of federal benefit	3.9%	4.0%	4.0%
Permanent differences	(4.6)%	(1.0)%	(3.3)%
Research and development credit	10.5%	7.3%	6.3%
Change in valuation allowance	(45.6)%	(22.9)%	(29.3)%
Stock-based compensation and 162(m) adjustment	(5.3)%	(5.0)%	(2.0)%
Provision to return adjustments	0.2%	(2.8)%	—%
Embedded derivative and warrant liabilities	16.6%	—%	—%
Other	3.0%	(0.8)%	3.1%
Effective income tax rate	(0.3)%	(0.2)%	(0.2)%

As of December 31, 2024, 2023 and 2022, we had U.S. federal net operating loss carryforwards of approximately $728.1 million, $768.5 million and $737.4 million, respectively, which may be able to offset future income tax liabilities. Of the $728.1 million carryforward as of December 31, 2024, $476.4 million of the carryforward has an indefinite life and $251.7 million will expire at various dates through 2037. As of December 31, 2024, 2023 and 2022, we had U.S. state net operating loss carryforwards of approximately $645.2 million, $655.7 million and $616.4 million, respectively, which may be available to offset future state income tax liabilities and expire at various dates through 2044. As of December 31, 2024, 2023 and 2022, we did not have any foreign net operating loss carryforwards to offset future foreign income tax liabilities.

As of December 31, 2024, 2023 and 2022, we had federal research and development and orphan drug tax credit carryforwards of approximately $107.3 million, $99.3 million and $90.9 million, respectively, available to reduce future tax liabilities, which expire at various dates through 2044. As of December 31, 2024, 2023 and 2022, we had state research and development tax credit carryforwards of approximately $13.1 million, $11.9 million and $12.0 million, respectively, available to reduce future tax liabilities, which expire at various dates through 2039. We completed a study of research and development tax credits through December 31, 2022 and adjusted our deferred tax asset for the results of that study. For the years ended December 31, 2024 and 2023, we generated research credits but have not conducted a study to document the qualified activities. This study may result in an adjustment to our research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against our research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of us immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. Previously, we have completed several financings since our inception, which have resulted in changes in control as defined by Sections 382 and 383 of the Internal Revenue Code. We reduced our deferred tax assets for tax attributes we believe will expire unused. In the future, we may complete financings that could result in a change in control, which will reduce our deferred tax assets for tax attributes we believe will expire unused due to the change in control limitations.

We will recognize interest and penalties related to uncertain tax positions in the income tax provision. As of December 31, 2024, 2023 and 2022, we had no accrued interest or penalties related to uncertain tax positions and no such amounts have been recognized.

We or one of our subsidiaries file income tax returns in the U.S. and various state and foreign jurisdictions. Our federal, state and foreign income tax returns are generally subject to tax examinations for the tax years ended December 31, 2021 through December 31, 2024. To the extent we have tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service, state or foreign tax authorities to the extent utilized in a future period.

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
3.1	Restated Certificate of Incorporation of the Registrant, as amended
3.2	Third Amended and Restated By-Laws of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on December 2, 2022)
4.1	Indenture (including form of Note) with respect to the Registrant's 3.00% convertible senior notes due 2025, dated as of October 16, 2018, between the Registrant and Wilmington Trust, National Association, as trustee (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on October 16, 2018)
4.2	Description of Securities Registered under Section 12 of the Exchange Act
4.3	Form of Warrant to Purchase Common Stock to be issued pursuant to the Securities Purchase Agreement (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on December 5, 2022)
4.4	Common Stock Purchase Warrant, dated August 1, 2023, issued to Healthcare Royalty Partners III, L.P. (incorporated by reference to Exhibit 4.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 2, 2023)
4.5	Indenture (including form of Note) with respect to the Registrant's 6.00% Convertible Senior Notes due 2029, dated as of May 13, 2024, between the Registrant, the guarantors party thereto and Wilmington Savings Fund Society, FSB, as trustee and collateral agent (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on May 14, 2024)
4.6	Form of Warrant to Purchase Common Stock (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on May 14, 2024)
10.1*	2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 28, 2013)
10.2*	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 28, 2013)
10.3*	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan adopted August 25, 2020 (incorporated by reference to Exhibit 10.9 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 2, 2020)
10.4*	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan adopted August 25, 2020 (incorporated by reference to Exhibit 10.10 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 2, 2020)
10.5*	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan adopted August 25, 2020 (incorporated by reference to Exhibit 10.11 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 2, 2020)
10.6*	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan adopted January 24, 2022 (incorporated by reference to Exhibit 10.11 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 1, 2022)
10.7*	2022 Equity Incentive Plan (incorporated by reference to Appendix A to the Registrant's Definitive Proxy Statement on Schedule 14A (File No. 001-36167) filed with the Commission on April 8, 2022)
10.8*	Amendment No. 1 to the 2022 Equity Incentive Plan (incorporated by reference to Appendix A to the Registrant's Definitive Proxy Statement on Schedule 14A (File No. 001-36167) filed with the Commission on April 11, 2023)
10.9*	Amendment No. 2 to the 2022 Equity Incentive Plan (incorporated by reference to Appendix A to the Registrant's Definitive Proxy Statement on Schedule 14A (File No. 001-36167) filed with the Commission on April 19, 2024)
10.10*	Form of Stock Option Agreement under the 2022 Equity Incentive Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 4, 2022)

10.11*	Form of Restricted Stock Unit Agreement under the 2022 Equity Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 4, 2022)
10.12*	Form of Restricted Stock Unit Agreement (Time Vested) under the 2022 Equity Incentive Plan adopted February 9, 2023 (incorporated by reference to Exhibit 10.14 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on February 17, 2023)
10.13*	Form of Restricted Stock Unit Agreement (Performance Vested) under the 2022 Equity Incentive Plan adopted February 9, 2023 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on February 15, 2023)
10.14*	Form of Nonstatutory Stock Option Agreement for Inducement Grants adopted August 25, 2020 (incorporated by reference to Exhibit 10.12 to the Registrant's Quarterly Report on Form 10-Q (File No.001-36167) filed with the Commission on November 2, 2020)
10.15*	2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.17 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 1, 2022)
10.16*	Amendment No. 1 to the 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 99.3 to Registrant's Registration Statement on Form S-8 (File No. 333-265386) filed with the Commission on June 3, 2022)
10.17*	Amendment No. 2 to the 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.20 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on February 17, 2023)
10.18*	Amendment No. 3 to the 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 99.4 to the Registrant's Registration Statement on Form S-8 (File No. 333-282994) filed with the Commission on November 5, 2024)
10.19*	Form of Stock Option Agreement under 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.18 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 1, 2022)
10.20*	Form of Restricted Stock Unit Agreement under 2022 Inducement Stock Incentive Plan (incorporated by reference to Exhibit 10.19 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 1, 2022)
10.21*	Form of Restricted Stock Unit Agreement (Time Vested) under the 2022 Inducement Stock Incentive Plan adopted February 9, 2023 (incorporated by reference to Exhibit 10.23 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on February 17, 2023)
10.22*	Amended & Restated 2013 Employee Stock Purchase Plan (incorporated by reference to Appendix B to the Registrant's Definitive Proxy Statement on Schedule 14A (File No. 001-36167) filed with the Commission on April 11, 2023)
10.23*	Amendment No. 1 to the Amended & Restated 2013 Employee Stock Purchase Plan (incorporated by reference to Appendix B to the Registrant's Definitive Proxy Statement on Schedule 14A (File No. 001-36167) filed with the Commission on April 19, 2024)
10.24*	Karyopharm Therapeutics Inc. Annual Bonus Plan (incorporated by reference to Exhibit 10.28 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on February 29, 2024)
10.25*	Form of Indemnification Agreement between the Registrant and each of its Directors (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)
10.26*	Non-Employee Director Compensation Policy (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 8, 2024)
10.27*	Promotion Letter, dated as of August 5, 2022, between the Registrant and Stuart Poulton (incorporated by reference to Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 4, 2023)
10.28*	Offer Letter, dated as of January 13, 2022, between the Registrant and Stuart Poulton (incorporated by reference to Exhibit 10.6 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 4, 2023)

10.29*	Promotion Letter, dated as of December 31, 2021, between the Registrant and Sohanya Cheng (incorporated by reference to Exhibit 10.7 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 4, 2023)
10.30*	Offer Letter, dated as of June 1, 2021, between the Registrant and Sohanya Cheng (incorporated by reference to Exhibit 10.8 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 4, 2023)
10.31*	Offer Letter, dated as of April 28, 2021, between the Registrant and Richard Paulson (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on May 3, 2021)
10.32*	Offer Letter, dated February 3, 2019, between the Registrant and Michael Mason (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on February 25, 2019)
10.33*	Letter Agreement, dated as of August 31, 2020, between the Registrant and Michael Mason (incorporated by reference to Exhibit 10.4 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on August 31, 2020)
10.34*	Offer Letter, dated as of April 4, 2022, between the Registrant and Reshma Rangwala (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 8, 2024)
10.35*	Offer Letter, dated as of December 19, 2024, between the Registrant and Lori Macomber (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on January 2, 2025)
10.36*	Transition Agreement, dated as of August 29, 2024, between the Registrant and Michael Mason (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on August 29, 2024)
10.37*	Consulting Agreement, dated as of August 29, 2024, between the Registrant and Michael Mason (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on August 29, 2024)
10.38*	Nonstatutory Stock Option Agreement, dated February 25, 2019, between the Registrant and Michael Mason (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on February 25, 2019)
10.39	Office Lease Agreement between NS Wells Acquisition LLC and the Registrant, dated March 27, 2014 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on April 1, 2014)
10.40	First Amendment to Lease, dated December 31, 2014, by and between the Registrant and NS Wells Acquisition LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on January 5, 2015)
10.41	Second Amendment to Lease, dated October 22, 2015, by and between the Registrant and NS Wells Acquisition LLC (incorporated by reference to Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 9, 2015)
10.42	Third Amendment to Lease, dated February 28, 2018, by and between the Registrant and AG-JCM Wells Avenue Property Owner, LLC (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 10, 2018)
10.43	Fourth Amendment to Lease, dated June 6, 2018, by and between the Registrant and AG-JCM Wells Avenue Property Owner, LLC (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2018)
10.44	Fifth Amendment to Lease, dated as of August 13, 2020, by and between the Registrant and AG-JCM Wells Avenue Property Owner, LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 2, 2020)
10.45	Sixth Amendment to Lease, dated as of November 5, 2024 by and between the Registrant and TCD 234 MA WELLS PROPERTY LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on November 8, 2024)

10.46	Open Market Sale Agreement[SM], dated as of February 17, 2023, by and between the Registrant and Jefferies LLC (incorporated by reference to Exhibit 1.2 to the Registrant's Registration Statement on Form S-3 (File No. 333-269846) filed with the Commission on February 17, 2023)
10.47†	License Agreement, dated May 23, 2018, by and between the Registrant and Antengene Therapeutics Limited (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2018)
10.48**	Amendment to License Agreement, dated May 1, 2020, by and between Antengene Therapeutics Limited and the Registrant (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 4, 2020)
10.49	Parent Company Guarantee, dated May 23, 2018, by and between the Registrant and Antengene Therapeutics Limited (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2018)
10.50**	License Agreement, dated as of December 17, 2021, between the Registrant and Berlin-Chemie AG (Menarini Group) (incorporated by reference to Exhibit 10.41 to the Registrant's Annual Report on Form 10-K (file No. 001-36167) filed with the Commission on March 1, 2022)
10.51	Amendment No. 1 to License Agreement, dated May 19, 2022, by and between the Registrant and Berlin-Chemie AG (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 4, 2023)
10.52	Amendment No. 2 to License Agreement, dated March 14, 2023, by and between the Registrant and Berlin-Chemie AG (incorporated by reference to Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on May 4, 2023)
10.53**	Revenue Interest Financing Agreement, dated September 14, 2019, between the Registrant and HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 4, 2019)
10.54	Second Amendment to Revenue Interest Financing Agreement, dated as of August 1, 2023, by and among the Registrant, Karyopharm Europe GmbH, HealthCare Royalty Partners III, L.P., HealthCare Royalty Partners IV, L.P., HCRP Overflow Fund, L.P., HCR Stafford Fund, L.P., HCR Canary Fund, L.P., HCR Potomac Fund, L.P., HCR Molag Fund, L.P., HealthCare Royalty Management, LLC and HCR Collateral Management, LLC (incorporated by reference to Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 2, 2023)
10.55**	Omnibus Amendment to Transaction Documents, dated as of June 23, 2021, by and among the Registrant, Karyopharm Europe GmbH, Karyopharm Therapeutics (Bermuda) Ltd., HealthCare Royalty Partners III, L.P., HealthCare Royalty Partners IV, L.P., HCRP Overflow Fund, L.P., HCR Stafford Fund, L.P., HCR Canary Fund, L.P., HCR Potomac Fund, L.P., HCR Molag Fund, L.P., HealthCare Royalty Management, LLC and HCR Collateral Management, LLC (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on June 24, 2021)
10.56	Second Omnibus Amendment to Transaction Documents, dated May 8, 2024, between the Registrant, the investors party thereto, HealthCare Royalty Management, LLC, HCR Collateral Management LLC, and HCR Karyopharm SPV, LLC (incorporated by reference to Exhibit 10.4 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on May 14, 2024)
10.57	Securities Purchase Agreement, dated December 5, 2022 by and among the Registrant and the other parties thereto (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on December 5, 2022)
10.58	Registration Rights Agreement, dated December 5, 2022 by and among the Registrant and the other parties thereto (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on December 5, 2022)
10.59	Credit Agreement, dated as of May 8, 2024, between the Registrant, the guarantors party thereto, the lenders party thereto, and Wilmington Savings Fund Society, FSB, as administrative agent and collateral agent (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on May 14, 2024)

10.60	Form of Exchange Agreement, dated May 8, 2024, by and among the Registrant and the other parties thereto (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on May 14, 2024)
10.61	Form of Registration Rights Agreement, dated May 13, 2024, by and among the Registrant and the other parties thereto (incorporated by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on May 14, 2024)
19.1	Insider Trading Policy
21.1	Subsidiaries of the Registrant
23.1	Consent of Ernst & Young LLP (Independent registered public accounting firm for the Registrant)
31.1	Certification of Chief Executive Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification of Executive Vice President, Chief Financial Officer and Treasurer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1	Certifications pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of The Sarbanes-Oxley Act of 2002, by Richard Paulson, President and Chief Executive Officer of the Registrant, and Lori Macomber, Executive Vice President, Chief Financial Officer and Treasurer of the Registrant
97*	Dodd-Frank Compensation Recovery Policy (incorporated by reference to Exhibit 97 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on February 29, 2024)
101.INS	The instance document does not appear in the interactive data file because its XBRL tags are embedded within the inline XBRL document.
101.SCH	Inline XBRL taxonomy Extension Schema with embedded Linkbases document
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101)

† Confidential treatment has been granted as to portions of the exhibit.
* Indicates a management contract or compensatory plan or arrangement.
** Certain portions of this exhibit (indicated by "***" or "**") have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

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.

Date: February 19, 2025

KARYOPHARM THERAPEUTICS INC.
By: /s/ Richard Paulson
Richard Paulson
President and Chief Executive Officer and Director
(Principal Executive Officer)

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Richard Paulson Richard Paulson	President and Chief Executive Officer and Director (Principal Executive Officer)	February 19, 2025
/s/ Lori Macomber Lori Macomber	Executive Vice President, Chief Financial Officer and Treasurer (Principal Financial Officer)	February 19, 2025
/s/ Kristin Abate Kristin Abate	Vice President, Chief Accounting Officer and Assistant Treasurer (Principal Accounting Officer)	February 19, 2025
/s/ Garen G. Bohlin Garen G. Bohlin	Director	February 19, 2025
/s/ Barry E. Greene Barry E. Greene	Director	February 19, 2025
/s/ Mansoor Raza Mirza Mansoor Raza Mirza, M.D.	Director	February 19, 2025
/s/ Christy J. Oliger Christy J. Oliger	Director	February 19, 2025
/s/ Deepika R. Pakianathan Deepika R. Pakianathan, Ph.D.	Director	February 19, 2025
/s/ Chen Schor Chen Schor	Director	February 19, 2025
/s/ Zhen Su Zhen Su, M.D.	Director	February 19, 2025

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