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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, 2020

☐ **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.☒

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, 2020 was approximately $1.32 billion. 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 16, 2021: 74,634,291.

Documents incorporated by reference:

Portions of the registrant's Proxy Statement for its 2021 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, 2020, 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 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.

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.

Risks Related to Commercialization and Product Development

- If we are unable to successfully commercialize XPOVIO or other products or product candidates in and outside of the U.S., our business, financial condition and future profitability will be materially harmed.
- XPOVIO faces substantial competition.
- If our clinical trials fail to demonstrate safety and efficacy 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 or our collaborators may not receive regulatory approvals for the commercialization of some or all of our or their product candidates in a timely manner, or at all.
- Serious adverse or unacceptable side effects related to XPOVIO or future products or product candidates 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 COVID-19 pandemic has adversely disrupted, and is expected to continue to adversely disrupt, our operations.
- 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.
- Our approved products may not receive coverage or may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives.
- Product liability lawsuits against us could divert our resources, result in substantial liabilities and limit commercialization of XPOVIO or any of our other products.
- Any business that we conduct outside of the U.S. may be adversely affected by international risks and uncertainties.

Risks Related to Regulatory Matters

- We may not be able to utilize accelerated development pathways to obtain regulatory approval, orphan drug exclusivity or certain other designations for our product candidates, which may result in delays receiving necessary marketing approvals, if approval is received at all.
- Our ability to commercialize our products may be limited by the terms of their respective regulatory approvals and ongoing regulation of our products.
- We and/or our collaborators may not obtain marketing approval in foreign jurisdictions.
- Current and future legislation may negatively impact (i) our and/or our collaborators' ability to obtain marketing approval, commercialize our products and obtain reimbursement for our products; (ii) the prices we or they obtain; and (iii) the costs for our products.
- Our failure to comply with any (i) post-approval development and regulatory requirements; (ii) reporting and payment obligations under governmental drug pricing programs; (iii) applicable anti-kickback, fraud and abuse and other healthcare laws and regulations; (iv) global privacy and data security requirements; or (v) environmental, health and safety laws and regulations may have a material adverse effect on our business, financial condition or results of operations.
- Our employees, independent contractors, consultants and vendors may engage in misconduct or other improper activities, which could cause significant liability for us.
- Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates outside of the U.S. and require us to develop and implement costly compliance programs.

- 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.
- We are subject to governmental export and import controls that could impair our ability to compete in international markets and subject us to liability if we are not in compliance with applicable laws.

Risks Related to Our Financial Position and Capital Requirements

- We may never achieve or maintain profitability and will need additional funding to achieve our business objectives, which may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our product candidates.
- We may not be able to satisfy our indebtedness, on a timely basis or at all, and we may be negatively impacted by various covenants and accounting methods related to our debt.
- Our business, financial condition and stock price may be impacted by unstable market and economic conditions.

Risks Related to Our Dependence on Third Parties

- 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.

Risks Related to Our Intellectual Property

- If we are unable to obtain and maintain patent protection for our product candidates and other discoveries, or the scope of the patent protection obtained is not sufficiently broad, our ability to successfully commercialize our 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.

Risks Related to Employee Matters and Managing Growth

- We may not be able to retain our Chief Executive Officer, our President and Chief Scientific Officer and other key executives and to attract, retain and motivate qualified personnel.
- Drs. Kauffman and Shacham are married to each other, and the separation or divorce of the couple could adversely affect our business.
- We have expanded and expect to continue to expand our development, regulatory and sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.
- Information technology system failures or security breaches may materially adversely affect our business and operations.

Risks Related to Our Common Stock

- Provisions in our charter and under Delaware law could make an acquisition of us more difficult and may prevent attempts by our stockholders to replace or remove our current management.
- The price of our common stock has been and may continue to be volatile.
- Securities or other litigation could result in substantial costs and may divert management’s time and attention from our business.
- We have broad discretion in the use of our cash, cash equivalents and investments and may not use them effectively.
- If we identify a material weakness in our internal controls 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.
- 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 ability to use our net operating loss carryforwards and tax credit carryforwards to offset future taxable income may be subject to certain limitations, and changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

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 transport for the treatment of cancer and other diseases. 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 **S**elective **I**nhibitor of **N**uclear **E**xport ("SINE") compounds that inhibit the nuclear export protein exportin 1 ("XPO1"). These SINE compounds, representing 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, were the first oral XPO1 inhibitors to receive marketing approval. Our lead asset, XPOVIO® (selinexor), 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:

- 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 supported by data from the BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) study (the "BOSTON Study").
- 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. We refer to myeloma that is refractory to these five agents as penta-refractory. Approval in this indication was supported by data from the STORM (**S**elinexor **T**reatment of **R**efractory **M**yeloma) study (the "STORM Study").
- 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 supported by data from the SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study (the "SADAL Study"). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

The commercialization of XPOVIO, for both the multiple myeloma and DLBCL indications, is currently supported by sales representatives and nurse liaisons 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, healthcare providers and patients about XPOVIO's clinical profile and unique mechanism of action as we expand XPOVIO into the second-line plus multiple myeloma market and continue to penetrate the third-line DLBCL market.

XPOVIO also received its first regulatory approval outside the U.S. with an approval received in February 2021 by our partner Promedico Ltd., a member of the Neopharm Group ("Promedico"), for the treatment of patients with multiple myeloma and DLBCL, in Israel. In addition, in January 2021, the European Medicines Agency's ("EMA") Committee for Medicinal Products for Human Use ("CHMP") adopted a positive opinion recommending the conditional approval of NEXPOVIO®(selinexor), the expected brand name for selinexor in Europe, based on the results of the Phase 2b STORM Study, which studied selinexor in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two PIs, two IMiDs and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. We expect a final decision from the European Commission (the "EC") on our Marketing Authorization Application ("MAA") by April 2021. A favorable decision based on our submission through the centralized procedure would be valid in all 27 European

Union ("EU") member countries as well as the European Economic Area countries of Iceland, Liechtenstein and Norway. Further, we plan to submit a second regulatory filing to the EMA (Type II variation) by April 2021 based on the data from the Phase 3 BOSTON Study, which evaluated once-weekly NEXPOVIO in combination with once-weekly Velcade® and low-dose dexamethasone in patients with multiple myeloma after at least one prior therapy with the goal of further expanding the global reach of NEXPOVIO to additional patients in need of new treatment options.

Our focus is on marketing XPOVIO in its currently approved indications as well as seeking the regulatory approval and potential commercialization of selinexor as an oral agent in additional cancer indications with significant unmet medical need. We plan to continue to conduct clinical trials and 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. Thus, we are advancing our clinical development program for selinexor in the areas of multiple hematological malignancies and solid tumors, among others, including the following ongoing or planned selinexor studies:

- Phase 3 SIENDO (**S**elinexor/Placebo After Combination Chemotherapy **I**n Patients with Advanced or Recurrent **ENDO**metrial Cancer) study evaluating once weekly selinexor versus placebo as maintenance therapy in patients with endometrial cancer after first- or second-line chemotherapy (the "SIENDO Study");
- Phase 2/3 trial evaluating the combination of selinexor and R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) in patients with relapsed or refractory DLBCL. The Phase 3 portion of the study will evaluate the selected dose (as identified in the Phase 2 study) of selinexor or matching placebo given with the standard combination immunochemotherapy R-GDP to patients with at least one prior therapy and who are ineligible for high dose chemotherapy and cell-based intervention such as chimeric antigen receptor T-cell therapy ("CAR-T") (the "XPORT-DLBCL-030 Study");
- Phase 1b/2 STOMP (**S**elinexor and Backbone **T**reatments **o**f **M**ultiple Myeloma **P**atients) multi-arm study to evaluate combinations of selinexor with standard therapies in multiple myeloma (the "STOMP Study");
- Phase 1/2 study of selinexor in combination with standard of care therapy in patients with newly diagnosed or recurrent glioblastoma ("GBM") (the "XPORT-GBM-029 Study");
- Phase 1/2 study of selinexor in combination with ruxolitinib in treatment naïve patients with myelofibrosis ("MF") (the "XPORT-MF-034 Study");
- Phase 2 study of selinexor versus treatment per physician's choice in participants with previously treated MF (the "XPORT-MF-035 Study"); and
- Phase 1/2 study to assess the preliminary anti-tumor activity of selinexor in combination with docetaxel in patients with non-small cell lung cancer ("NSCLC") and with pembrolizumab in patients with colorectal cancer ("CRC"). (the "XPORT-STP-027 Study").

Additionally, we expect to initiate a number of new clinical trials in 2021, including a Phase 3 study evaluating selinexor in combination with pomalidomide in patients with relapsed or refractory multiple myeloma as well as new Phase 1 and 2 studies evaluating selinexor in patients with a variety of solid tumor indications, including metastatic melanoma, lung cancer and colorectal cancer. A number of these studies will be investigating the treatment of selinexor in combination with other standard of care anti-cancer drugs.

In addition to selinexor, we are also advancing a pipeline of other novel product candidates including the following oral SINE compounds:

- **Eltanexor**: We are currently focusing on the development of eltanexor to treat patients with myelodysplastic syndrome ("MDS") as well as evaluating additional, potential solid tumor indications for future clinical development.

- **Verdinexor**: We are evaluating verdinexor as a potential therapy for viral, rare disease and autoimmune indications in humans, and our partner Anivive Life Sciences, Inc. ("Anivive") is evaluating verdinexor as a therapy for cancers in companion animals. As discussed below, in January 2021, Anivive received conditional approval from the FDA for LAVERDIA™-CA1 (verdinexor) as the first oral treatment of canine lymphoma.
- **KPT-9274:** We are evaluating KPT-9274, an oral inhibitor of p21-activated kinase 4 ("PAK4") and nicotinamide phosphoribosyltransferase ("NAMPT"), to treat patients with hematologic or solid tumors. In July 2020, the first patient was dosed in a Phase 1/2 clinical study of KPT-9274 in combination with an anti-PD1 monoclonal antibody.

Key 2020 and Recent Highlights

XPOVIO Franchise

- Received FDA approval in December 2020 (three months ahead of the FDA's Prescription Drug User Fee Act target action date) for XPOVIO to treat multiple myeloma after at least one prior therapy based on the BOSTON Study, which satisfied the post-approval requirement of a confirmatory trial for the July 2019 accelerated approval of XPOVIO based on the STORM Study.
- Received FDA accelerated approval in June 2020 for XPOVIO for the 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.
- National Comprehensive Cancer Network ("NCCN") added three different XPOVIO combination regimens to its NCCN Guidelines for previously treated multiple myeloma in December 2020.
- Recognized XPOVIO net revenue of $76.2 million in 2020.
- Saw nearly 3,900 XPOVIO prescriptions filled in 2020, driven by demand across both academic and community-based physicians.
- Grew prescription refill rates for XPOVIO with the average number of prescriptions per patient reaching approximately three as of December 31, 2020.
- Received a positive opinion from the CHMP in January 2021 recommending the conditional approval of NEXPOVIO in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two PIs, two IMiDs and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.
- European Hematology Association and European Society for Medical Oncology ("ESMO") added selinexor to European multiple myeloma treatment guidelines in November 2020.

Selinexor Pipeline

- Met primary endpoint in Phase 3 SEAL (**Se**linexor in **A**dvanced **L**iposarcoma) study in liposarcoma (the "SEAL Study") in November 2020 with statistically significant increase in progression free survival ("PFS") in patients with unresectable dedifferentiated liposarcoma. Data was presented at the Connective Tissue Oncology Society 2020 Annual Meeting.
- Passed planned futility analysis in the SIENDO Study in November 2020 with a recommendation from the Data and Safety Monitoring Board (the "DSMB") to continue without the need to add additional patients to the trial or to amend the study protocol. Top line data is expected to be available in the second half of 2021.
- Dosed first patient in February 2021 in Phase 3 confirmatory trial in the XPORT-DLBCL-030 Study.
- Dosed first patient in June 2020 in the XPORT-GBM-029 Study.

Collaborations

- Entered into an exclusive distribution agreement in February 2020 with Promedico for the commercialization of XPOVIO in Israel and the Palestinian Authority. In February 2021, Promedico received a principal approval letter from the Israeli Ministry of Health granting approval of XPOVIO for the treatment of patients with either multiple myeloma or DLBCL in Israel.
- Entered into a collaboration, option and license agreement in April 2020 with Curadev Pharma Pvt Ltd ("Curadev"), a privately-owned biotechnology company, to identify and co-develop novel small molecules against various biological targets for the treatment of cancer and other major diseases.
- Amended our license agreement with Antengene Therapeutics Limited ("Antengene") in May 2020 to expand Antengene's development and commercial rights to our compounds in parts of Asia, Australia and New Zealand and received approximately $10.0 million in regulatory milestones from Antengene in December 2020 following certain regulatory filings by Antengene for selinexor in both multiple myeloma and DLBCL indications in Australia, Singapore and South Korea.
- Entered into a Cooperative Research and Development Agreement ("CRADA") with the National Cancer Institute's ("NCI") Cancer Therapy Evaluation Program in July 2020 to collaborate on studies to investigate the safety and efficacy of selinexor in various oncology indications.
- Entered into an exclusive distribution agreement in December 2020 with FORUS Therapeutics Inc. ("FORUS") for the commercialization of XPOVIO in Canada and received a $5.0 million upfront payment in December 2020.
- Received, through our partner Anivive, conditional approval from the FDA in January 2021 for LAVERDIA™-CA1 (verdinexor) as the first oral treatment for canine lymphoma.
- Entered into collaboration agreements with partners outside of the U.S. to establish paid named patient programs to provide opportunities to reach additional patients and generate revenue from selinexor indications that have been approved in the U.S. as a bridge to approval in certain geographies.

Corporate Highlights

- Completed a follow-on offering in March 2020 pursuant to which we issued an aggregate of 7,187,500 shares of common stock and received aggregate net proceeds of approximately $161.8 million.
- Amended our Open Market Sale Agreement with Jefferies LLC, as agent, in May 2020, pursuant to which we increased the maximum aggregate offering price of shares of our common stock that we may issue and sell from time to time under the agreement from $75.0 million to up to $175.0 million.
- Ended 2020 with $276.7 million in cash, cash equivalents, restricted cash and investments.

Our Strategy

The critical components of our business strategy are to:

- ***Maximize the Commercial Value of XPOVIO and Our Other Product Candidates.*** We are executing on our U.S. commercial capabilities and supporting the ongoing launch of XPOVIO in the U.S. We plan to continue to penetrate the U.S. commercial market and further educate the medical community about the clinical data that support XPOVIO as a treatment for multiple myeloma and DLBCL. Outside of the U.S., subject to approval of selinexor, we will either work with existing and potential partners to establish the requisite commercial infrastructure.
- ***Continue to Develop and Seek Regulatory Approvals of Selinexor Outside of the U.S.*** We, or our current or future partners, continue to seek regulatory approvals of selinexor outside of the U.S. for each indication in which we receive favorable results in a registration-enabling clinical trial.

- ***Maintain Our Competitive Advantage and Scientific Expertise in the Field of Nuclear Transport.*** To further our understanding of the role nuclear transport plays in the underlying biology of cancer, as well other diseases, we plan to continue research in the field of nuclear transport and related areas, primarily by fostering relationships with scientific advisors and physicians. We continue to explore a variety of standard and novel combinations of other anti-cancer agents with our SINE inhibitors, and these non-clinical studies are anticipated to provide support for new clinical investigations.
- ***Continue Developing our Pipeline of Novel Product Candidates.*** To date, we have identified several drug candidates: our oral SINE compounds selinexor, eltanexor and verdinexor and KPT-9274. We may also identify or in-license novel product candidates for development in oncology or other indications in the future.
- ***Maximize the Value of Our SINE Compounds in Non-Oncology Indications through Collaborations.*** We may seek to enter into global or regional development, marketing, and commercialization collaboration arrangements for our SINE compounds in non-oncology indications.

Our XPOVIO Program to Treat Cancer

Overview

According to the World Health Organization, cancer is the second leading cause of death globally and in 2020 was responsible for more than one in six deaths, or an estimated 10 million deaths. Additionally, cancer is one of the most important health issues facing patients in the U.S. The American Cancer Society ("ACS") estimates that in 2021 there will be nearly 1.9 million new cancer cases in the U.S., with approximately 608,000 Americans expected to die of cancer.

Cancer is a disease characterized by unregulated cell growth. Cancer cells develop when DNA inside the nucleus of normal cells accumulates damage in genes that regulate cell growth and survival. In healthy cells, proteins called tumor suppressor proteins located in the cell nucleus help prevent the accumulation of DNA damage (mutations, chromosomal translocations and other abnormalities) by monitoring DNA 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. Accumulation of tumor suppressor proteins in the nucleus of cancer cells allows them to perform their normal role of detecting DNA damage, thereby inhibiting a cancer cell's ability to divide, and promoting apoptosis.

Many tumor suppressor proteins can only function properly when they are located inside of a cell's nucleus. Proteins, however, are not made inside the nucleus but rather are made outside of the nucleus in an area called the cytoplasm. A membrane, called the nuclear membrane, separates the nucleus from the cytoplasm. Larger nuclear proteins, including tumor suppressor proteins, must be transported from the cytoplasm where they are made into the nucleus to perform their functions in keeping a cell healthy. Similarly, when they have completed their normal functions, these proteins are typically exported back into the cytoplasm. Proteins move between the nucleus from 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, including many other proteins and ribonucleic acids ("RNAs"), 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 evade detection from the body's own defense mechanisms is by removing tumor suppressor proteins from within the cell nucleus via an overproduction of a specific chaperone protein called

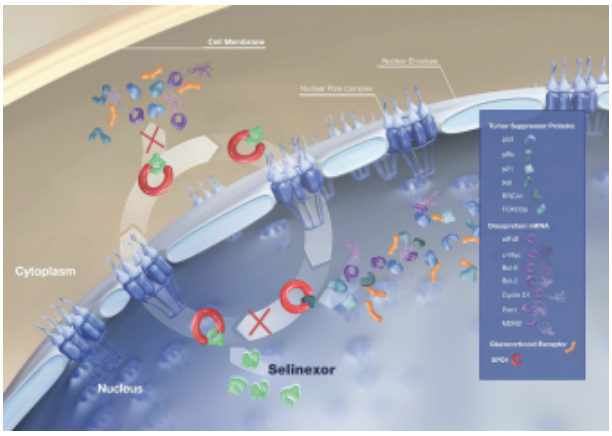
XPO1. XPO1 is one of eight exportins that have been identified in human cells, and it exports over 220 proteins referred to as its "cargo proteins." In particular, XPO1 appears to be the sole exporter for most of the tumor suppressor proteins including p53, p73, p21, p27, APC, FOXO, pRB and survivin. 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 mRNAs that code for these proteins ("eIF4E" and also called the "mRNA cap binding protein"). eIF4E binds to the mRNAs for many growth-regulating proteins, including c-myc, bcl-2, bcl-6 and cyclin D, and depends on XPO1 to help carry these growth-promoting mRNAs from the nucleus into the cytoplasm where the mRNAs are efficiently translated into proteins. XPO1 also exports the anti-inflammatory (and anti-tumor) protein IkB, which inhibits a protein called NF-kB. NF-kB 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.

In nearly all cancer cells, XPO1 levels are reported to be elevated when compared to their healthy cell counterparts. Therefore, these elevated levels of XPO1 in cancer cells mediate the rapid export of tumor suppressor proteins as well as IkB and eIF4E out of the nucleus and can lead to reduced monitoring for DNA damage, the normal triggering of apoptosis and increased NF-kB activity. Higher levels of XPO1 expression in cancer cells is also generally correlated with resistance to chemotherapy and poor prognosis in patients.

Mechanism of Action of Our SINE Compounds—Inhibition of XPO1

XPOVIO and our product candidates are novel therapies that are first-in-class, oral SINE compounds specifically designed to force nuclear accumulation in the levels of multiple tumor suppressor and growth regulatory proteins. One of the ways a cell regulates the function of a particular protein is by controlling that protein's location within the cell since certain functions may only occur within a particular location in the cell. As described above, the nuclear pore is a complex gate between the nucleus and cytoplasm, regulating the import and export of most large molecules, called macromolecules, including many proteins, into and out of the nucleus. In healthy cells, nuclear transport, both into and out of the nucleus, is a normal and regular occurrence that is tightly regulated and requires the presence of specific carrier proteins. XPO1 mediates the transport of the majority of tumor suppressor proteins and appears to be the only mediator of nuclear export for these proteins.

XPO1 inhibitors, such as XPOVIO, block the nuclear export of tumor suppressor, growth-regulating, and anti-inflammatory proteins, leading to accumulation of these proteins in the nucleus and enhancing their anti-cancer activity in the cell. The forced nuclear retention of these proteins can counteract a multitude of the oncogenic pathways that allow cancer cells with severe DNA damage to continue to grow and divide in an unrestrained fashion. Because normal cells have little or no DNA damage, 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 and oncoprotein mRNAs.



We believe that selinexor's novel mechanism of action, oral administration and low levels of major organ toxicities observed to date in patients treated with selinexor, along with encouraging efficacy data, support the potential for selinexor's 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 assess a cell's DNA, our SINE compounds may provide therapeutic benefits across a broad range of both hematological and solid tumor malignancies and can potentially benefit a wider range of patients. Additionally, and as supported by its mechanism of action, and preclinical, clinical and post-approval data, we believe that selinexor has shown additive or synergistic benefit with approved and experimental therapies in treating cancer patients and, therefore, has the potential to serve as a backbone therapy across multiple hematological and solid tumor malignancies as part of a variety of combination therapies.

Update to NCCN Treatment Guidelines for Patients with Previously Treated Multiple Myeloma

In December 2020, the NCCN added three different XPOVIO combination regimens to its Clinical Procedure Guidelines in Oncology for Previously Treated Myeloma (the "NCCN Guidelines"). The NCCN Guidelines are a comprehensive set of guidelines detailing the sequential management decisions and interventions that currently apply to 97% of cancers affecting patients in the U.S. and are intended to ensure that all patients receive preventive, diagnostic, treatment and supportive services that will most likely lead to optimal outcomes. The XPOVIO regimens added to the NCCN Guidelines include: (i) selinexor/bortezomib/dexamethasone (once-weekly), which also received a Category 1 recommendation, which represents the highest designation assigned by NCCN, indicating the recommendation is based upon high-level evidence and that there is uniform NCCN consensus that the intervention is appropriate; (ii) selinexor/daratumumab/dexamethasone; and (iii) selinexor/pomalidomide/dexamethasone, which is an all-oral treatment regimen.

Summary of Our Pipeline and Key Clinical Trials

Oral selinexor is being evaluated in multiple later-phase clinical trials in patients with hematological and solid tumor malignancies, often in the relapsed and/or refractory setting. In general, relapsed disease refers to disease that progresses following the expiration of a specified period of time after discontinuation of therapy and refractory disease refers to disease that progresses while the patient is on therapy or within a specified period of time after discontinuation of therapy. Key clinical trials of selinexor are summarized in the charts below. In addition to these studies, there are several ongoing investigator-sponsored clinical trials being conducted in a variety of hematological and solid tumor malignancies.

HEMATOLOGICAL MALIGNANCIES

We are currently evaluating XPOVIO in certain hematological malignancies, including multiple myeloma, DLBCL and MF.

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 disease, kidney disease and immunodeficiency. Multiple myeloma is one of the most common types of blood cancer in the U.S. According to the ACS, nearly 35,000 new cases of multiple myeloma will be diagnosed in the U.S. in 2021. It is more common in elderly patients, and most frequently diagnosed among people between ages 65 to 74 years with a median age at diagnosis of 69 years. Despite recent therapeutic advances, there is currently no cure and most patients' disease will typically progress following treatment with currently available therapies.

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 ("ASCT"), which is restricted to healthier, often younger patients, and the subsequent introduction of IMiDs, such as Revlimid® (lenalidomide) and Pomalyst® (pomalidomide), and PIs such as Velcade® (bortezomib), Kyprolis® (carfilzomib), and Ninlaro®(ixazomib). Three monoclonal antibodies, Darzalex®(daratumumab), SARCLISA® (isatuximab-irfc), and Empliciti®

(elotuzumab), and one monoclonal antibody with a toxin conjugate, BLENREP (belantamab mafodotin-blmf), have also been approved, as has the histone deacetylase inhibitor Farydak® (panobinostat). The introduction of non-chemotherapeutic agents has led to a significant increase in the survival of patients with multiple myeloma. Although a wide variety of newly approved or experimental therapies are being used to treat relapsed and/or refractory patients, including new PIs (oprozomib and marizomiband cellular therapies such as CAR-T therapy), nearly all patients will eventually relapse and succumb to their disease. With nearly 12,500 deaths from multiple myeloma in the U.S. alone estimated for 2021 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.

Supporting Studies

The BOSTON Study

The December 2020 FDA approval of XPOVIO's expanded indication as a treatment for patients with multiple myeloma after at least one prior therapy was supported by the results of the BOSTON Study, a multi-center, Phase 3, randomized study conducted at over 150 clinical sites internationally, which evaluated 402 adult patients with relapsed or refractory multiple myeloma who had received one to three prior lines of therapy. The study was designed to compare the efficacy, safety and certain health-related quality of life parameters of once-weekly XPOVIO in combination with once-weekly Velcade® plus low-dose dexamethasone (the "XVd Arm") versus twice-weekly Velcade® plus dexamethasone (the "Vd Arm"). The primary endpoint of the study was PFS and key secondary endpoints included overall response rate ("ORR") and the rate of peripheral neuropathy ("PN"), among others. Additionally, the BOSTON Study 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 ("IRC").

Although the study had one of the highest proportions of patients with high-risk cytogenetics (~50%) as compared with other Velcade®-based studies in previously treated multiple myeloma, 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 (hazard ratio 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 ³ Very Good Partial Response ("VGPRs") 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 Complete Response ("CR") or a Stringent Complete Response ("sCR") as compared to 10% of patients receiving Vd therapy. All responses were confirmed by an IRC. Rates of PN were significantly lower for patients receiving XVd therapy compared to those receiving Vd therapy (32% vs. 47%). In addition, PN rates ³ Grade 2 were also significantly lower in the XVd Arm compared to the Vd Arm (21% vs. 34%).

The most common adverse reactions (³20%) in patients with multiple myeloma 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 (³10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia. In the BOSTON Study, 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%.

Certain subgroup populations of the BOSTON Study were evaluated and reported at the American Society of Hematology ("ASH") 2020 Annual Meeting. We believe these subgroup evaluations of XVd therapy showed consistent PFS benefit and higher ORR compared to Vd therapy, including in evaluations of the safety and efficacy of XPOVIO (i) in patients previously treated with PIs; (ii) according to the number of prior lines of therapy or prior treatment with Revlimid®; (iii) in patients with high risk cytogenetics; and (iv) based on age (patients younger than 65 years old versus older than 65 years old) or by frailty level (frail versus fit).

The STORM Study

The July 2019 FDA approval of XPOVIO to treat patients with penta-refractory multiple myeloma was supported by the results of the STORM Study. This indication was approved under accelerated approval based on response rate. The BOSTON Study served as the confirmatory trial under the FDA's Accelerated Approval Program and, therefore, the approval of the BOSTON supplemental new drug application in December 2020 fulfilled the accelerated approval requirements of the STORM FDA approval.

The STORM Study 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 study had prior treatment with the two PIs, Velcade® and Kyprolis®, the two IMiDs, Revlimid® and Pomalyst®, and the anti-CD38 monoclonal antibody Darzalex®, 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." In a subset of 83 patients, their disease was designated as penta-refractory myeloma. In addition to multiple-refractory disease, patients in the STORM Study had rapidly progressing myeloma, with a median 22% increase in disease burden in the 12 days from screening to initial therapy.

For the STORM Study's primary endpoint, oral selinexor achieved an ORR of 26%, including two (2%) sCRs, six (5%) VGPRs, and 24 (20%) partial responses ("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 ("IMWG") criteria was observed in 16 (13%) patients and 48 patients (39%) 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 IRC consisting of four independent experts in the treatment of multiple myeloma.

Median DOR was 4.4 months. PFS was 3.7 months and overall survival ("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 (³20%) in patients with multiple myeloma 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 Study, 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 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 Study 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. The ORR in this patient population was 25.3%. Our request for conditional approval in Europe is based upon this same patient population that served as the basis for XPOVIO's accelerated FDA approval in the U.S.

The STOMP Study

The STOMP Study, an ongoing multi-arm Phase 1b/2 clinical trial in patients with relapsed or refractory multiple myeloma, is evaluating selinexor and low-dose dexamethasone in combinations with standard therapies, such as Pomalyst®, Kyprolis®, Revlimid®, Velcade®, and Darzalex®. We presented the following updated clinical data from the STOMP Study at the ASH 2020 Annual Meeting in December 2020, demonstrating that selinexor and low-dose dexamethasone plus standard anti-myeloma therapies exhibit encouraging response rates in these combination regimens:

(1) Selinexor in Combination with Pomalyst® and Low-dose Dexamethasone ("XPd") in Patients with Relapsed or Refractory Multiple Myeloma

In this all oral arm of the Phase 1b/2 STOMP Study, selinexor is being evaluated in combination with Pomalyst® 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. Of note, 25% of the population enrolled in the study had previously received Darzalex®. The recommended Phase 2 dose ("RP2D") was determined to be 60 mg of XPOVIO orally once-weekly, four mg of Pomalyst® orally once-daily and 40 mg once weekly or 20 mg twice weekly of dexamethasone orally. The following table is a summary of the efficacy results:

Best Responses[1] in Evaluable XPd Patients as of November 14, 2020[2]						
Category	**N**	**ORR***	**CR**	**VGPR**	**PR**	**Median PFS**
Pomalyst® naïve or non-refractory	46	25 (54%)	1 (2%)	9 (20%)[3]	15 (33%)[4]	12.3 months
Pomalyst® refractory	14	5 (36%)	—	1 (7%)	4 (29%)	Not reported
RP2D	20	12 (60%)	—	6 (30%)	6 (30%)	Not reached[5]
All patients	60	30 (50%)	1 (2%)	10 (17%)	19 (32%)	12.2 months

* ORR = CR+VGPR+PR

1 Responses were adjudicated according to the IMWG criteria.

2 Based on interim unaudited data.

3 Two VGPRs were unconfirmed.

4 One PR was unconfirmed.

5 Median follow-up time for 20 patients at the RP2D was 2.5 months; median follow-up time for all 60 patients was 12.2 months.

Among the patients evaluated for safety as of the data cutoff date, the most common treatment-related adverse events ("AEs") were cytopenias, along with gastrointestinal and constitutional symptoms; most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (60%), fatigue (51%), decreased appetite (44%), weight loss (38%) and diarrhea (29%), and were primarily grade 1 and 2 events. The most common treatment-related Grade 3 and 4 AEs were neutropenia (54%), anemia (33%), and thrombocytopenia (32%).

Based on these Phase 2 results, we plan to initiate a Phase 3 study investigating the XPd combination in 2021. Historical clinical trials evaluating the efficacy of Pomalyst® and low-dose dexamethasone in less heavily pretreated populations (i.e., without prior Darzalex® therapy) have demonstrated an ORR of 29% and median PFS of 3.6 months, as highlighted in the Pomalyst® U.S. Full Prescribing Information.

(2) Selinexor in Combination with Kyprolis® and Low-dose Dexamethasone ("XKd") in Patients with Relapsed or Refractory Multiple Myeloma

In this arm of the Phase 1b/2 STOMP Study, oral selinexor is being evaluated in combination with Kyprolis® and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma who have received at least two prior therapies, including a PI, one or more IMiDs (e.g., Revlimid® or Pomalyst®) or Darzalex®. In these heavily pretreated patients, 100% had previously received Velcade®, 96% had previously received Revlimid®, 67% had previously received Pomalyst® and 63% had previously received Darzalex®. The RP2D was determined to be 80 mg of XPOVIO orally once-weekly, 56 mg/m^2 of Kyprolis® once-weekly and 40 mg once weekly or 20 mg twice weekly of dexamethasone orally and enrollment continues using this regimen. The median PFS was 23.7 months for all patients. The following table is a summary of the efficacy results:

Best Responses[1] in Evaluable XKd Patients as of October 1, 2020[2]					
Category	**N**	**ORR**	**CR**	**VGPR**	**PR**
All	24	18 (75%)	5 (21%)	8 (33%)	5 (21%)

1 Responses were adjudicated according to the IMWG criteria.
2 Based on interim unaudited data.

Among the patients evaluated for safety as of the data cutoff date, the most common treatment-related AEs were cytopenias, along with gastrointestinal, constitutional and other symptoms; most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (71%), fatigue (58%), decreased appetite (50%) and weight loss (46%), and were mostly Grade 1 and 2 events. The most common treatment-related Grade ³3 AEs included thrombocytopenia (58%), anemia (21%) and leukopenia (13%).

We are encouraged by these results, which indicate that the once weekly combination of XKd may induce beneficial response rates in patients with heavily pretreated double or triple class refractory multiple myeloma.

(3) Selinexor in Combination with Revlimid® and Low-dose Dexamethasone ("XRd") in Patients with Newly Diagnosed and Relapsed or Refractory Multiple Myeloma

In this all oral arm of the Phase 1b/2 STOMP Study, selinexor is being evaluated in combination with Revlimid® and low-dose dexamethasone in patients with newly diagnosed or previously treated multiple myeloma. The previously treated patients received at least one prior therapy, which may include prior Revlimid®, as long as the patient's myeloma was not refractory to Revlimid®. The RP2D was determined to be 60 mg of XPOVIO orally once-weekly, 25 mg of Revlimid® orally once daily, and 40 mg once weekly or 20 mg twice weekly of dexamethasone orally. The following table is a summary of the efficacy results:

Best Responses[1] in Evaluable XRd Patients as of October 1, 2020[2]					
Category	**N**	**ORR**	**CR**	**VGPR**	**PR**
Revlimid®-naïve relapsed or refractory myeloma	12	11 (92%)	1 (8%)	4 (33%)	6 (50%)[3]
Revlimid®-treated/refractory myeloma	8	1 (13%)	—	—	1 (13%)
Newly diagnosed (efficacy evaluable)	7[4]	7 (100%)	1 (14%)	4 (57%)[5]	2 (29%)

1 Responses were adjudicated according to the IMWG criteria.
2 Based on interim unaudited data.
3 Two PRs were unconfirmed.
4 One patient's efficacy not evaluable due to withdrawal of consent during cycle 1.
5 One VGPR was unconfirmed.

Responses were highly durable with four relapsed or refractory patients remaining on study with PFS of greater than 35 months and two newly diagnosed patients remaining on study with PFS of greater than 24 months.

Among the newly diagnosed patients evaluable for safety, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms; most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were fatigue (63%), weight loss (63%), diarrhea (63%), nausea (50%) and insomnia (38%) and were mostly Grade 1 and 2 events. The most common Grade ³3 AEs were neutropenia (75%), anemia (50%) and thrombocytopenia (38%).

Among the relapsed or refractory patients evaluable for safety, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms; most were manageable with dose modifications and/or standard supportive care. The most common non-hematologic treatment-related AEs were nausea (58%), fatigue (54%), decreased appetite (50%), weight loss (42%), and diarrhea (33%), and were mostly Grade 1 and 2 events. The most common Grade ³3 AEs were thrombocytopenia (63%), neutropenia (63%), anemia (17%) and fatigue (17%).

We are encouraged by these results, which indicate that the all oral regimen of weekly selinexor with standard Revlimid® and dexamethasone may induce high response rates with good tolerability.

Diffuse Large B-Cell Lymphoma

Overview

DLBCL is a form of Non-Hodgkin's lymphoma ("NHL"), 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. NHL is one of the most common cancers in the U.S., accounting for approximately 4% of all cancers. In 2021, the ACS estimates that more than 81,000 people will be diagnosed with NHL and approximately 20,000 deaths will result from the disease. DLBCL is the most common and most aggressive type of NHL, making up approximately 18,000 of the new cases diagnosed annually in the U.S. Most often, newly diagnosed patients are currently cured with front-line (typically "R-CHOP" chemotherapy). Despite the recent approval of CAR-T therapy, many patients with relapsed or refractory DLBCL are not medically stable enough to undergo CAR-T therapy and additional treatment options are necessary to address this continued unmet medical need.

In 2019, the FDA granted accelerated approval to the triplet therapy polatuzumab vedotin, bendamustine, rituximab, known as PBR, for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified after at least two prior therapies. The FDA also approved Monjuvi® (tafasitamab-cxix) in July 2020 in combination with lenalidomide for the treatment of adult patients with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for ASCT.

Supporting Studies

The SADAL Study

In June 2020, the FDA approved XPOVIO as the only 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 supported by the results of the SADAL Study, 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, XPOVIO 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.

The most common adverse reactions (³20%) in patients with DLBCL who received XPOVIO 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 (³15%) are thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia. In the SADAL Study, 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 XPOVIO. Treatment discontinuation rate due to adverse reactions was 17%.

Other DLBCL Studies

During 2021, we expect to conduct the following two studies in DLBCL:

- **The XPORT-DLBCL-030 Study**, which will serve as a confirmatory study for the June 2020 FDA accelerated approval of XPOVIO to treat DLBCL based on the SADAL Study, is a Phase 2/3 multi-center, randomized study evaluating the combination of selinexor and R-GDP in patients with relapsed or refractory DLBCL. The Phase 3 portion of the study will evaluate the selected dose (as identified in the Phase 2 study) of selinexor or matching placebo given with the standard combination immunochemotherapy R-GDP to patients with at least one prior therapy and who are ineligible for high dose chemotherapy and cell-based intervention such as CAR-T. The primary endpoint of the Phase 3 portion of the XPORT-DLBCL-030 Study is PFS. The first patient in this study was dosed in February 2021.
- **The XPORT-DLBCL-025 Study** is a Phase 1/2 multi-arm study of selinexor in combination with backbone treatments or novel therapies for the treatment of DLBCL. The first clinical trial site for the XPORT-DLBCL-025 Study was activated in November 2020 and we plan to initiate this study in 2021. This study will inform the use of selinexor with a variety of additional agents including novel/novel combinations for the treatment of DLBCL.

Myelofibrosis

Primary MF is a rare blood cancer in which excessive scar tissue (fibrosis) forms in the bone marrow and impairs its ability to produce normal blood cells. As a result, blood cell production may move to the spleen (causing spleen enlargement) or to other areas of the body. The incidence of MF is estimated to be approximately 1.5 cases per 100,000 people in the U.S. with a median OS of 69 months. MF is more common in older patients with a median age at diagnosis of approximately 65 years.

Allogeneic hematopoietic stem cell transplantation (“HSCT”) is currently the only treatment for MF that can provide a clinical cure; patients who are not good candidates for HSCT should receive a JAK2 inhibitor, such as ruxolitinib or fedratinib to reduce spleen volume and improve symptoms. However, not all patients respond adequately to JAK2 inhibitors, and some patients cannot tolerate treatment or progress on treatment.

In preclinical studies, XPO1 inhibition by selinexor selectively suppressed colony formation in MF cells, including those exposed to prior JAK2 inhibitors, compared with normal CD34+ cells and enhanced ruxolitinib-mediated growth inhibition and cancer cell death. In an MF mouse model, the combination of selinexor and ruxolitinib improved responses compared with monotherapy, including reductions of mutant cells and restoration of splenic architecture. This formed the preclinical rationale for investigating selinexor in patients with MF. In 2021, we plan to initiate the XPORT-MF-034 Study, a Phase 1/2 open-label, multicenter study of selinexor to evaluate the safety and efficacy of selinexor in combination with ruxolitinib in treatment naïve patients with MF and the XPORT-MF-035 Study, a Phase 2, randomized, open-label, multicenter study to evaluate the safety and efficacy of single agent selinexor versus treatment of physician’s choice in patients with previously treated MF.

Other Hematologic Malignancies

Myelodysplastic Syndromes

MDS is a group of hematologic malignancies whereby the bone marrow does not make enough healthy blood cells (white blood cells, red blood cells, and platelets) and there are abnormal cells in the blood and/or bone marrow. The median OS of patients with high-risk MDS refractory to hypomethylating agents is less than six months and, currently, no standard therapy for such patients exists. In August 2020, safety and efficacy results from a single-arm investigator sponsored Phase 2 study of selinexor in patients with MDS or oligoblastic acute myeloid leukemia refractory to hypomethylating agents were published in the journal *The Lancet Haematology*. According to *The Lancet Haematology* publication, preclinical studies have shown that inhibition of XPO1 causes nuclear accumulation of p53 and disruption of NF-kB signaling, both relevant targets for MDS. In the 23 patients evaluable in the clinical study, the ORR was 26% (95% CI 10 – 48); six patients had a marrow complete remission and an additional 12 patients (52%, 95% CI 31 – 73) had stable disease. The most common grade 3 or 4 AEs were thrombocytopenia (32%; 8/25 patients) and hyponatraemia (20%; 5/25 patients). There were no drug-related serious AEs and no treatment-related deaths. Based on these data and the data from a Phase 1 study of eltanexor, as discussed further below, we intend to enroll additional patients in single-agent and combination studies to evaluate eltanexor to treat MDS.

SOLID TUMOR MALIGNANCIES

Solid tumors represent the vast majority of cancer incidences. Given the large patient population with solid tumors and the mechanistic activity of selinexor that makes it potentially suitable for treating any type of cancer, we are developing selinexor to potentially play a meaningful role across multiple solid tumor indications, either alone or in combination as a backbone therapy. We have seen encouraging single-agent data for selinexor in a variety of solid tumors including PRs and durable stable disease (“SD”) with disease control greater than three months. Our Phase 2/3 study in patients with dedifferentiated liposarcoma demonstrated statistically significant prolonged PFS of heavily pretreated patients and our Phase 2 studies of selinexor in gynecological malignancies and GBM also demonstrated anti-cancer activity, including bona fide PRs as well as prolonged SD. Given the promising single-agent activity in difficult-to-treat indications and the potential to enhance activity in combination with existing therapies, we are currently developing selinexor in unmet needs such as liposarcoma, endometrial cancer and GBM.

In addition, we believe that the results of clinical data from investigator-sponsored studies evaluating selinexor in combination with certain established cancer therapies warrant further research into the potential utility of selinexor in solid tumors and will help us further prioritize future clinical development activities. For example, in September 2020, clinical data were presented at the ESMO Virtual Congress from advanced solid tumor studies evaluating selinexor in combination with established cancer therapies including combination data with (i) pembrolizumab for the treatment of melanoma; (ii) carboplatin and paclitaxel for the treatment of advanced or metastatic solid tumors; and (iii) topotecan for the treatment of advanced or metastatic solid tumors.

We plan to continue to develop selinexor in combination with standard of care anti-cancer drugs, including immunotherapies, with a particular interest in lung cancer, brain cancer, metastatic melanoma and colorectal cancer.

Liposarcoma

Overview

Liposarcoma is a rare cancer of connective tissues that resemble fat cells under a microscope and represents up to 18% of all soft tissue sarcoma, or approximately 2,000 new cases in the U.S. per year. Current treatment of liposarcoma largely includes a combination of radiation therapy and surgery, with or without chemotherapy. Dedifferentiated liposarcoma is an aggressive form of soft tissue sarcoma that is resistant to both standard

chemotherapy and radiation. Liposarcoma has a particularly high rate of recurrence following surgery, especially in cases involving the abdomen. Except for cases that are cured with surgery, most patients with metastatic liposarcoma will succumb to this disease, and novel therapies are needed.

The SEAL Study

In November 2020, we announced positive top-line results from the Phase 3 portion of the randomized, double blind, placebo-controlled, cross-over, SEAL Study conducted in North America and Europe in patients with unresectable dedifferentiated liposarcoma. Patients in this study were randomized 2:1 to receive either oral selinexor (60 mg twice weekly) until disease progression or intolerability, or placebo. The SEAL Study met its primary endpoint of a statistically significant increase in PFS (hazard ratio=0.70; p=0.023) as assessed by the Independent Central Radiological Review committee based on RECIST v1.1. We believe these data indicate that treatment with selinexor reduced the risk of disease progression by approximately 30%, compared to placebo. The trial allowed patients on placebo with objective progression to cross over to the selinexor treatment arm. Among those patients who received selinexor, there was a trend towards an improvement in the median OS compared to those patients who began on the placebo arm of the study and never crossed over to the selinexor treatment arm of the study. The safety profile for selinexor was consistent with previous clinical studies with fewer hematologic and infection-related AEs as compared to selinexor studies in patients with multiple myeloma and DLBCL.

Based on preliminary regulatory feedback, expected cost, commercial potential, and strategic priorities, we are currently evaluating the optimal approach and next steps towards making selinexor available to patients with dedifferentiated liposarcoma, including potentially pursuing a strategy of presenting clinical data to support the use of selinexor in patients with unresectable dedifferentiated liposarcoma as a medically accepted indication in published drug compendia.

Endometrial Cancer

Overview

Endometrial cancer, also called uterine cancer, occurs when cells in the endometrium, which is the inner lining of uterus, begin to grow out of control. In the U.S., endometrial cancer is the most common cancer of the female reproductive organs. The ACS estimates that there will be approximately 60,000 new cases of endometrial cancer diagnosed in 2021 in the U.S., with approximately 11,600 deaths. Endometrial cancer affects mainly post-menopausal women and the average age of women diagnosed with endometrial cancer is 60. Endometrial cancer is often detected at an early stage because it frequently produces abnormal vaginal bleeding. There are currently five different types of standard treatment for patients with endometrial cancer; surgery, radiation therapy, chemotherapy, hormone therapy and targeted therapy.

The SIENDO Study

The SIENDO Study is an ongoing multicenter, randomized, double-blinded Phase 3 study evaluating the efficacy and safety of selinexor versus placebo as a maintenance therapy in patients with advanced or recurrent endometrial cancer following at least one prior platinum-based combination chemotherapy treatment. Participants with primary stage IV or recurrent disease who had a PR or CR after at least 12 weeks of standard taxane-platinum combination chemotherapy are randomized in a 2:1 manner to receive either maintenance therapy of 80 mg of XPOVIO taken once per week or placebo, until disease progression. The primary endpoint in the study is PFS with the goal of the study demonstrating a hazard ratio of 0.6.

In November 2020, following a pre-specified interim futility analysis for the SIENDO Study, the DSMB recommended that the study should continue, as previously planned, without the need for adding additional patients to the trial or amending the study protocol. As of the date of the planned futility analysis, 109 patients of the expected 248 patients had been enrolled in the trial. We currently expect to report topline data from the SIENDO Study in the second half of 2021.

This trial was designed based on the data from a Phase 2, open-label study of efficacy and safety of oral selinexor in patients with heavily pre-treated, progressive gynecological cancers (the "SIGN Study"). In December 2019, the full results from the SIGN Study in patients with recurrent gynecological malignancies were published in *Gynecologic Oncology*. According to the published data, the SIGN Study showed selinexor's promising anti-tumor activity and disease control in gynecological malignancies. Of the 66 patients with ovarian cancer, 20 patients (30%) had disease control, meaning PR or SD for at least 12 weeks, including seven patients (11%) with a PR. The median DOR for patients that achieved a PR was 7.4 months. Median PFS for all patients with ovarian cancer was 2.6 months and median OS was 7.3 months. Of the 23 patients with endometrial cancer, eight (35%) had disease control (three PRs and five with SD for at least 12 weeks). Median PFS for the endometrial cancer arm was 2.8 months and median OS was 7.0 months. Across all arms, the most common AEs were nausea (71%), fatigue (68%), decreased appetite (57%), vomiting (53%), weight loss (48%), anemia (36%), and thrombocytopenia (34%), which were managed with supportive care and dose modifications. Notably, fewer Grade 3 and 4 AEs occurred in patients receiving once weekly compared to twice weekly selinexor, with equivalent efficacy.

Glioblastoma Multiforme

Overview

GBM is one of the most common and particularly aggressive forms of brain tumors of primarily glial cell origin, accounting for 48% of all primary malignant brain tumors. Patients with GBM face significant morbidity and mortality rates, with over 10,000 deaths per year in the U.S. GBM is an incurable disease and the prognosis for patients is typically poor due, in part, to its aggressive and extensive infiltration of surrounding central nervous system tissue and its frequent inaccessibility for surgical resection within the brain. In addition, the blood-brain barrier presents an obstacle for many chemotherapeutic agents, with only small, lipophilic molecules able to reach the tumor. The median age of diagnosis in patients is 64 years old, but GBM can occur at any age, including in childhood. Median survival in patients with newly diagnosed GBM is approximately 15 months and approximately five to seven months in patients with recurrent disease. GBM is a disease with high unmet need, with existing treatments having very limited success in increasing overall surviving rates. The current standard of care for GBM patients includes surgery, radiation therapy, and chemotherapy. Currently approved drug treatments for GBM include temozolomide and Avastin® (bevacizumab). Despite these treatment options, most patients diagnosed with GBM will quickly succumb to the disease and novel therapies are needed.

XPO1 is frequently overexpressed in both GBM and in high-grade gliomas and therefore may be an important, novel target in the treatment of patients with GBM. The degree of XPO1 over-expression correlates with higher tumor grade and poor overall patient survival. Nonclinical studies indicate that selinexor has potent anti-GBM activity as monotherapy and is synergistic when combined with radiation, temozolomide and lomustine. Additionally, in our previous clinical study known as the KING study, selinexor demonstrated that it crosses the blood-brain barrier with adequate intra-tumoral penetration and single-agent efficacy with durable response and disease stabilization in heavily pretreated GBM patients, which we believe supports the rationale for further clinical development of selinexor to treat patients with brain cancers.

The XPORT-GBM-029 Study

We are currently conducting a global Phase 1/2 clinical study evaluating oral selinexor in combination with standard of care therapy in patients with newly diagnosed or recurrent GBM, which is expected to enroll approximately 400 patients at clinical sites in the U.S., Europe, and Israel. In June 2020, we dosed the first patient in this study. This study is expected to be conducted in two phases: a Phase 1 dose finding study followed by a Phase 2 randomized efficacy exploration study, designed to independently evaluate three different combination regimens in three treatment arms in patients with newly diagnosed GBM (Arms A and B) or with recurrent GBM (Arm C). Arms A and B will investigate selinexor in combination with radiation therapy with or without the addition of temozolomide, while Arm C will evaluate the combination of selinexor and lomustine. The primary endpoints in the study are PFS in patients with newly diagnosed GBM and OS in patients with recurrent GBM.

OUR OTHER PIPELINE PROGRAMS

In addition to selinexor, we are also advancing a pipeline of novel drug candidates including our other oral SINE compounds eltanexor, verdinexor and KPT-9274.

Eltanexor (KPT-8602)

Eltanexor is a second-generation SINE compound that, like selinexor, selectively blocks the nuclear export protein XPO1. The mechanism of action for the biological (anti-cancer) activity of eltanexor is similar to selinexor. However, eltanexor differs from selinexor primarily because it has been confirmed to have much lower brain penetration in preclinical species, when compared with selinexor. Therefore, eltanexor may cause fewer side effects, particularly those mediated through the central nervous system such as nausea, fatigue and anorexia in humans. Following oral administration, animals treated with eltanexor showed a lower percentage of body weight loss and improved food consumption, as well as less "fatigue behavior," in comparison to animals similarly treated with selinexor. This allows for more frequent dosing of eltanexor, enabling a longer period of exposure at higher levels than is possible with selinexor. In many preclinical studies, an extended dosing regimen led to superior efficacy in comparison to selinexor treatment. As a result, we believe that eltanexor represents a potent, efficacious second-generation oral SINE compound and are currently evaluating its safety, tolerability and efficacy in humans.

We currently plan to focus our clinical development of eltanexor in patients with MDS and are conducting a first-in-human Phase 1/2 clinical trial for eltanexor in patients with relapsed or refractory multiple myeloma, metastatic colorectal cancer, metastatic castration resistant prostate cancer, and higher risk refractory MDS to determine the safety, preliminary efficacy, and RP2D of eltanexor in patients with these advanced cancers.

At the ASH 2019 annual meeting, positive data was presented from the Phase 1/2 study evaluating the safety, tolerability and anti-tumor activity of single-agent oral eltanexor (10 mg or 20 mg once-daily for five days per week) in elderly patients with higher-risk MDS with disease refractory to hypomethylating agents. Of the 15 patients evaluable for efficacy, seven patients had a marrow CR indicating an ORR of 47%. An additional five patients (33%) achieved SD as their best response for a total disease control rate of 80% in evaluable patients. Median OS in patients receiving a 20 mg dose was 10.6 months. The most common treatment-related AEs were hematologic, gastrointestinal and constitutional. The most common non-hematologic treatment-related AEs were nausea (45%), decreased appetite (40%), fatigue (35%), diarrhea (35%) and dysgeusia (25%); the vast majority were Grade 1 or 2. The most common Grade ³ 3 AEs were anemia (30%), neutropenia (25%), thrombocytopenia (20%) and leukopenia (15%). AEs were dose-dependent and generally managed with supportive care and dose modification. This Phase 1/2 study remains ongoing. Based on these data, we plan to amend the existing Phase 1/2 study protocol to evaluate eltanexor in combination with oral hypomethylating agents in patients with newly diagnosed or previously treated MDS. The novel combination arms are expected to begin enrollment in 2021.

Verdinexor (KPT-335)

Lymphoma in Companion Canines

We have used spontaneously occurring canine cancers as a surrogate model for human malignancies. It is widely known that canine lymphomas are similar in many ways to the non-Hodgkin's lymphomas in humans, display a comparable genetic profile and respond to chemotherapy in a fashion similar to their human counterparts. Lymphomas are one of the most common tumors in dogs and are very aggressive where, without treatment, the tumors are often fatal within weeks. The majority of canine lymphomas are DLBCL and most of the others are T-cell lymphomas. Given the similarities of dog and human lymphomas, prior to initiating clinical trials of selinexor in humans, we investigated verdinexor, a closely related, orally available SINE compound, in dogs with lymphomas.

In May 2017, we entered into an exclusive licensing agreement with Anivive, a privately-held biotech company focused on innovations in the veterinary drug and bioinformatics space, pursuant to which Anivive received worldwide rights to research, develop and commercialize verdinexor for the treatment of cancer in companion animals. In January 2021, Anivive received conditional FDA approval of LAVERDIA™-CA1 (verdinexor) to treat dogs with lymphoma through the Minor Use/Minor Species pathway, which is an option for drugs intended for minor uses in major species, such as dogs, or for minor species. Verdinexor is the first conditionally approved oral treatment for dogs with lymphoma. Tanovea-CA1, an injectable product, is currently the only other treatment for lymphoma in dogs. Anivive has five years to complete effectiveness studies to support a full approval of verdinexor in this indication.

The recent approval of verdinexor was supported by a Phase 2b clinical trial conducted with 58 pet dogs with B- or T-cell lymphoma who were either newly-diagnosed or who were in their first relapse after chemotherapy and were followed for at least eight months. Seventeen of the 58 dogs (29%) did not show progression of lymphoma for at least 56 days after taking verdinexor. Three of these dogs did not show any progression for at least 182 days. The most common adverse reactions associated with verdinexor were anorexia, vomiting, diarrhea, weight loss, lethargy, increased water intake, increased urination, elevated liver enzymes, and low platelet count.

Viral, Rare Disease and Autoimmune Indications

In addition to canine lymphoma, verdinexor is being evaluated as a potential therapy for viral, inflammatory, and autoimmune indications. Several autoimmune indications are driven by aberrant pro-inflammatory responses, particularly uncontrolled pro-inflammatory cytokine expression and NF-kB activation. These include systemic lupus erythematosus (“SLE”), a primary focus of our work with verdinexor. The National Institute of Health funded project completed preclinical evaluation of verdinexor as a treatment for SLE and positioned the SLE program as Investigational New Drug (“IND”) ready.

In addition, several viruses exclusively utilize XPO1 to shuttle cargos necessary for viral replication, such as viral and host proteins from the nucleus to the cytoplasm. Due to the stability of host gene targets compared to viruses which rapidly adapt for best fitness in hosts, targeting host genes may offer an approach to limit drug resistance.

In 2015, we conducted a randomized, double-blind, placebo-controlled, dose-escalating Phase 1 clinical trial of verdinexor in healthy human volunteers in Australia. This study was designed to evaluate the safety and tolerability of verdinexor in healthy adult subjects. Mild to moderate AEs of similar grade and in an equivalent percentage of patients as placebo were reported, and no serious or severe AEs were observed.

As part of an exclusive license agreement we entered into with Antengene in May 2018, and as amended in May 2020, Antengene maintains the exclusive rights to develop and commercialize 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. Antengene has reported that it intends to conduct clinical trials of verdinexor for the treatment of chronic active Epstein Barre infection and SLE.

We plan to continue to explore strategies to pursue the clinical development of verdinexor as a treatment for viral, inflammatory, and autoimmune indications, including potentially partnering with additional collaborators or through government-funded grant or contract opportunities.

KPT-9274

KPT-9274 is our first-in-class dual inhibitor of PAK4 and NAMPT. KPT-9274 is an orally bioavailable small molecule that we believe could play an important role in cancer development by targeting the two proteins PAK4 and NAMPT. PAK4 is a signaling protein regulating numerous fundamental cellular processes, including

intracellular transport, cellular division, cell shape and motility, cell survival, immune defense and the development of cancer. PAK4 interacts with many key signaling molecules involved in cancer such as beta-catenin, CDC42, Raf-1, BAD and myosin light chain. NAMPT, also known as PBEF or Visfatin, is a pleiotropic protein with intra- and extra-cellular functions as an enzyme, cytokine, growth factor, and hormone that can be found in complex with PAK4 in the cell. NAMPT is of interest as an oncology target because it catalyzes the rate-limiting step in one of the two intracellular salvage pathways that generate nicotinamide adenine dinucleotide, a universal energy- and signal-carrying molecule involved in mitochondrial function, energy metabolism, calcium homeostasis, antioxidation, and paradoxically generation of oxidative stress, gene expression, immunological functions, aging, and cell death.

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.

KPT-9274 is currently being evaluated in a Phase 1 open-label study in patients with advanced solid malignancies or non-Hodgkin's lymphoma. As of February 2021, patient enrollment continues in Part C of the trial evaluating the combination of KPT-9274 and Opdivo® (nivolumab) in patients with melanoma who progressed on an anti-PD-1 or anti-PD-L1 antibody in a prior line of therapy.

The Potential of Our SINE Compounds in Settings Beyond Oncology

In addition to cancer, our SINE compounds have demonstrated the potential to provide therapeutic benefit in a number of other indications, such as viral infections, neurological disorders, inflammation and autoimmune diseases. For example, in January 2018, we entered into an Asset Purchase Agreement with Biogen MA Inc., a subsidiary of Biogen Inc. ("Biogen"), pursuant to which Biogen acquired KPT-350, which has been renamed by Biogen as BIIB100, an IND application-ready, oral SINE compound with a preclinical data package supporting potential efficacy in a number of neuro-inflammatory conditions, as well as certain related assets with an initial focus in amyotrophic lateral sclerosis ("ALS"). XPO1 mediates the nuclear export of multiple proteins that impact neurological and inflammatory processes. Consequently, inhibition of XPO1 by BIIB100 has shown a reduction in inflammation and an increase in anti-inflammatory and neuroprotective responses. BIIB100 penetrates the blood brain barrier to a greater degree than other SINE compounds. Preclinical data generated largely by external collaborators show efficacy of BIIB100 and related SINE compounds in animal models of ALS, multiple sclerosis, traumatic brain injury, epilepsy, and other neuro-inflammatory indications. Biogen is currently conducting a Phase 1 double-blind, placebo-controlled, single-ascending-dose study to evaluate the safety, tolerability and pharmacokinetics and pharmacodynamics of BIIB100 administered orally to adult patients with ALS.

The accumulation of IkB in the nucleus inhibits NF-kB, which may be beneficial in overcoming chemotherapy resistance and in treating autoimmune, inflammatory, and neuro-inflammatory disease, has been detected in both preclinical models and in human cancer tissues from treated patients.

SINE compounds have also demonstrated activity in animal models of viral diseases, certain rare diseases and other indications, and we are continuing to develop programs in these areas largely through academic collaborations and non-dilutive funding opportunities with the intent to out-license these programs for clinical development and future commercialization.

Uncertainty Relating to the COVID-19 Pandemic

The COVID-19 pandemic has and will continue to affect economies and businesses around the world. We continue to closely monitor the impact of the COVID-19 pandemic on all aspects of our business, including the impact on our employees, patients and business operations. We have and may continue to experience disruptions in the future that could impact our results of operations, including product revenue, and financial condition. Although we do not currently expect that the ongoing COVID-19 pandemic will have a material impact on our business plans or results of operations, we are unable to predict the impact that the COVID-19 pandemic will have on our operating results and financial condition due to numerous uncertainties. These uncertainties include the availability and effectiveness of vaccines and therapeutics, the duration and scope of the pandemic, the severity of the virus, governmental, business or other actions, travel restrictions and social distancing, business closures or business disruptions, or changes to our operations, among others. We will continue to monitor the COVID-19 situation closely and intend to follow health and safety guidelines as they evolve. Further, the impacts of a potential worsening of global economic conditions and the continued disruptions to, and volatility in, the credit and financial markets, as well as other unanticipated consequences remain unknown. The situation surrounding the COVID-19 pandemic remains fluid and continues to rapidly evolve, and we are actively managing our response and assessing potential impacts to our operating results and financial condition, as well as adverse developments in our business.

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 when we believe the financial terms of the collaboration are favorable for meeting our short- and long-term strategic objectives. Currently, we maintain complete commercial rights to selinexor in the U.S., Europe, Japan, and Latin America and have entered into the following key agreements:

Antengene

In May 2020, we entered into an amendment of our May 2018 license agreement with 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"). Under the terms of the Original Antengene Agreement, in 2018 we received an upfront cash payment of $11.7 million. In June 2020, we received an additional $11.7 million upfront payment upon execution of the Amended Antengene Agreement.

During 2020 and early 2021, Antengene has progressed its development and regulatory plans and has submitted new drug applications ("NDAs") for selinexor to regulatory authorities in Singapore, Australia, Hong Kong, South Korea and China for relapsed or refractory multiple myeloma and/or relapsed or refractory DLBCL indications. In addition, Antengene is currently conducting two registrational Phase 2 clinical trials of XPOVIO in China for relapsed or refractory multiple myeloma and relapsed or refractory DLBCL and has initiated clinical trials for high prevalence cancer types in the Asia Pacific region including peripheral T-cell lymphoma and NK/T-cell lymphoma and KRAS-mutant non-small cell lung cancer.

In December 2020, we received approximately $10.0 million from Antengene upon the submission of certain of Antengene's recent NDAs and are entitled to receive additional milestone payments from Antengene if

certain development, regulatory and commercialization goals are achieved in the future. Finally, we will be 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, 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, a Neopharm Company

In February 2020, we entered into an exclusive distribution agreement with Promedico for the commercialization of XPOVIO in Israel and 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.

Biogen

In January 2018, we entered into an asset purchase agreement with Biogen pursuant to which Biogen acquired our oral SINE compound KPT-350, which has been renamed by Biogen as BIIB100, and certain related assets. We received a one-time upfront payment of $10.0 million in 2018 from Biogen and are eligible to receive additional payments of up to $207.0 million based on the achievement by Biogen of future specified development and commercial milestones. We are also eligible to receive tiered royalty payments that reach low double digits based on future net sales until the later of the tenth anniversary of the first commercial sale of the applicable product or the expiration of specified patent protection for the applicable product, determined on a county-by-country basis.

Anivive

In May 2017, we entered into an exclusive licensing agreement with Anivive pursuant to which Anivive received worldwide rights to research, develop and commercialize verdinexor for the treatment of cancer in companion animals. In 2017, we received an upfront payment of $1.0 million and a subsequent milestone payment of $250,000 and are eligible to receive up to $43.25 million in future regulatory, clinical and commercial milestone payments, assuming regulatory approval of verdinexor in both the U.S. and the EU. In addition, Anivive agreed to pay us up to low double-digit royalty payments based on future net sales of verdinexor. Verdinexor received conditional approval from the FDA in January 2021 as the first oral treatment for canine lymphoma. This approval triggered an additional milestone obligation to us of $500,000 in January 2021.

Curadev

In April 2020, we entered into a collaboration, option and license agreement with Curadev, a privately-owned biotechnology company, to identify and co-develop novel small molecules against various biological targets for the treatment of cancer and other major diseases**.** Under the terms of the agreement, we and Curadev have agreed to identify and develop small molecules against up to two targets. Curadev will conduct exploratory research, drug discovery and development for designated programs up to the conclusion of preclinical proof of concept studies, after which we will have an option to an exclusive license to develop and commercialize each target on a global basis. We and Curadev will co-fund and jointly oversee development up to the option exercise period.

CRADA with NCI

In July 2020, we entered into a CRADA with the NCI's Cancer Therapy Evaluation Program. Under the terms of the CRADA, the NCI will collaborate with us on studies to investigate the safety and efficacy of selinexor in various oncology indications, based on encouraging anti-tumor activity observed in earlier studies. As data from the NCI-sponsored studies and other Karyopharm-sponsored studies emerge, we plan to collaborate with the NCI on trials to complement and support the further development of selinexor that could address important patient unmet medical needs. The NCI may also support non-clinical studies to explore important future combinations of selinexor with other targeted or standard of care cancer agents.

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 2, 2021, we were the sole owner of 21 patents in the U.S. and we had 16 pending patent applications in the U.S., four pending international applications filed under the Patent Cooperation Treaty ("PCT"), 77 granted patents and 71 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 technology underlying such pending patent applications has been developed by us and was not acquired from any in-licensing agreement.

The intellectual property portfolios for our key products and product candidates as of February 2, 2021 are summarized below.

- **Selinexor (KPT-330)**: Our selinexor patent portfolio covers the composition of matter and methods of use of selinexor and verdinexor, as well as methods of making both, and consists of seven issued U.S. patents (two patents are specific to selinexor, two patents are specific to verdinexor, two patents cover both selinexor and verdinexor and the seventh patent covers polymorphs of selinexor), 34 issued foreign patents, 39 pending foreign patent applications, two pending U.S. non-provisional applications, one pending PCT application and four pending U.S. provisional patent applications. The PCT application provides the opportunity to seek protection in all PCT member states. Any patents that may issue in the U.S. as part of our selinexor patent portfolio, with the exception of a patent directed to the polymorphs of selinexor and a patent based on the pending PCT application, will expire in 2032, absent any terminal disclaimer, patent term adjustment due to administrative delays by the U.S. Patent and Trademark Office ("USPTO") or patent term extension under the Drug Price Competition and Patent

Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. Any patents that may issue in foreign jurisdictions will likewise expire in 2032. Any patents that may issue in the U.S. directed to the polymorphs of selinexor will expire in 2035, 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 2035. Any patents that may issue in the U.S. based on the pending PCT 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. If non-provisional patent applications claiming the benefit of the pending U.S. provisional patent applications referenced above are filed in 2021, any patents that may issue from such applications will expire no earlier than 2041.

- **Selinexor (Wound Healing)**: Our patent portfolio covering selinexor for wound healing, including acute and chronic wounds, covers methods of using selinexor or verdinexor for wound healing, including systemic and topical uses, and consists of one issued U.S. patent and one granted European patent. The U.S. patent will expire in 2034, absent any terminal disclaimer, patent term adjustment due to administrative delay by the USPTO or patent term extension under the Hatch-Waxman Act. The European patent will likewise expire in 2034.
- **Verdinexor (KPT-335)**: Our selinexor patent portfolio described above, with the exception of the applications directed to polymorphs of selinexor, the one pending PCT application and the four pending U.S. provisional applications, also covers both the composition of matter and methods of use of verdinexor, as well as methods of making verdinexor. There are four issued U.S. patents that cover verdinexor. One patent is specific to verdinexor, two patents cover both verdinexor and selinexor (also referenced above with respect to selinexor) and the other covers veterinary uses of verdinexor.
- **Eltanexor** (**KPT-8602)**: Our eltanexor patent portfolio covers both the composition of matter and methods of use of eltanexor, and consists of two issued U.S. patents, one pending non-provisional U.S. patent application, 14 issued foreign patents, 15 pending foreign patent applications and one pending PCT application. The PCT application provides the opportunity for seeking protection in all PCT member states. Any patents that may issue in the U.S. as part of our eltanexor patent portfolio, with the exception of a patent based on the pending PCT 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 issued in foreign jurisdictions will likewise expire in 2034. Any patents that may issue in the U.S. based on the pending PCT application will expire in 2039, 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 2039.
- **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 six issued U.S. patents, 11 issued foreign patents, one pending U.S. non-provisional patent application, and 15 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 eltanexor, and consists of seven pending U.S. provisional applications and two pending PCT applications. The PCT applications provide the opportunity for seeking protection in all PCT member states. Any patents that may issue in the U.S. based on the pending PCT Applications will expire no earlier than 2039 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 no earlier than 2039. If non-provisional patent applications claiming the benefit of the pending U.S. provisional applications referenced above are filed in 2021, any patents that may issue from such applications will expire no earlier than 2041.

In addition to the patent portfolios covering our key products and product candidates, as of February 2, 2021, our patent portfolio also includes five patents (U.S. Patent Nos. 8,513,230, 9,428,490, 9,550,757,10,526,295 and 10,709,606) and 17 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 our name and logo, and a combination of the two, XPOVIO, and PORE for our online portal. We also have pending applications to register two additional possible product names (currently refused), and KARYFORWARD and a KARYFORWARD logo for our financial aid and charitable services. Outside the U.S., XPOVIO is registered or pending in forty-six additional jurisdictions, and is registered in Katakana in Japan, Hangul in South Korea, and Chinese characters in Taiwan. The KARYFORWARD logo is registered or pending in four jurisdictions outside 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. 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 and the other indications on which we currently plan to focus, including many major pharmaceutical and biotechnology companies. To our knowledge, there is only one other XPO1 inhibitor in clinical development. In June 2020, The Menarini Group acquired Stemline Therapeutics, Inc., including its oral XPO1 inhibitor, felezonexor. The Menarini Group is continuing a Phase 1 dose-escalation trial to evaluate felezonexor in patients with advanced solid tumors.

Many of the companies against which we are competing or against which we may compete 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 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 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 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 and the other indications on which we currently plan to initially focus are currently 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 other product candidates or for XPOVIO/NEXPOVIO 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 a variety of 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 and the other indications on which we plan to focus. 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/NEXPOVIO competes with and, if approved, our other lead product candidates may compete with the investigational therapies and/or currently marketed products discussed below.

Multiple Myeloma

Many therapies are approved for use in patients with multiple myeloma. Our primary competitors in this indication, including the following, currently treat patients ranging from newly diagnosed patients to those with relapsed and/or refractory multiple myeloma and are indicated for use either as single agent and/or as combination therapies:

- **IMiDs**: Revlimid®(lenalidomide), Pomalyst®(pomalidomide) and Thalomid®(thalidomide), all marketed by Celgene Corporation (“Celgene”) /Bristol-Myers Squibb Company (“BMS”);
- **PIs**: Velcade®(bortezomib) marketed by Takeda Pharmaceutical Company Limited (“Takeda”) in the U.S. and Janssen Pharmaceutical K.K. (“Janssen”) outside of the U.S., Ninlaro®(ixazomib) marketed by Takeda and Kyprolis®(carfilzomib) marketed by Amgen Inc. (“Amgen”);
- **Monoclonal antibodies**: Darzalex®(daratumumab) marketed by Janssen, Empliciti®(elotuzumab) marketed by BMS and Sarclisa®(isatuximab-irfc) marketed by Sanofi S.A. (“Sanofi”);
- **Antibody Drug Conjugate**: BLENREP (belantamab mafodotin-blmf) marketed by GlaxoSmithKline plc (“GSK”);
- **Histone Deacetylase inhibitor**: Farydak®(panobinostat) marketed by Novartis AG (“Novartis”); and
- **Anthracycline**: Doxil® (liposomal doxorubicin) marketed by Janssen.

Several other anti-cancer agents are in mid to late-stage development for the treatment of patients with multiple myeloma, including:

- **Anti-BCMA directed CAR-T therapies:** ciltacabtagene autoleucel (cilta-cel, previously known as JNJ-68284528/ JNJ-4528) from Janssen and Legend Biotech Corporation, ide-cel (previously known as bb2121) from bluebird bio, Inc. (“bluebird bio”)/Celgene/BMS, orvacabtagene Autoleucel (orva-cel, previously known as JCARH125) from Juno Therapeutics, Inc./Celgene/BMS and P-BCMA-101 from Janssen/Poseida Therapeutics, Inc.;
- **Immunomodulator**: Iberdomide (previously known as CC-220, cereblon E3 ligase modulator) from Celgene/BMS and Opdivo® (nivolumab) from BMS;
- **Alkylating agent**: Ygalo® (melphalan flufenamide) from Oncopeptides AB;
- **BCL-2 inhibitor**: Venclexta® (venetoclax) from AbbVie Inc. (“AbbVie”)/Genentech USA (“Genentech”);

- **Anti-CD38 Monocolonal antibodies**: mezagitamab (previously known as TAK-079) from Takeda;
- **Bi-specific antibodies**: teclistamab (previously known as JNJ-64007957) from Johnson & Johnson/Janssen, CC-93269 from bluebird bio/Celgene/BMS, AMG420 from Amgen, REGN5458 from Regeneron Pharmaceuticals, Inc. ("Regeneron") and PF-06863135 from Pfizer Inc.; and
- **Other molecules**: Imbruvica® (ibrutinib) from Pharmacyclics LLC ("Pharmacyclics")/AbbVie/Janssen, nirogacestat (previously known as PF 3084014) from Springworks Therapeutics, Inc./Janssen, plitidepsin from Pharma Mar S.A. ("Pharma Mar"), masitinib from AB Science Group, filanesib from Array Biopharma Inc. and ricolinostat from Celgene.

DLBCL

The initial therapy for DLBCL typically consists of multi-agent cytotoxic drugs in combination with the monoclonal antibody 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. and/or Europe and/or 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. These recently approved therapeutic interventions are also being evaluated via late-stage development in earlier lines of therapy for the treatment of patients with DLBCL:

- **CD19-directed CAR-T therapies:** Kymriah® (tisagenlecleucel) marketed by Novartis, Yescarta® (axicabtagene ciloleucel) marketed by Kite Pharma, Inc., a Gilead Company, and Breyanzi® (lisocabtagene maraleucel; liso-cel) marketed by BMS;
- **CD79b-directed antibody-drug conjugate**: Polivy® (polatuzumab vedotin-piiq) marketed by Genentech F. Hoffmann-La/Roche AG ("Roche"); and
- **CD19-directed cytolytic antibody:** Monjuvi® (tafasitamab-cxix, previously known as MOR208 in combination with lenalidomide) marketed by MorphoSys AG/Incyte Corporation ("Incyte").

Other agents are listed in the NCCN and/or the ESMO guidelines for use after one to two prior therapies, although they have not been formally approved by the FDA including: Revlimid® (lenalidomide), Imbruvica® (ibrutinib) from Pharmacyclics/Abbvie, 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:

- **Immune modulator:** Keytruda® (pembrolizumab) ("Keytruda") from Merck & Co. ("Merck") and Imfinzi® (durvalumab) from AstraZeneca plc ("AstraZeneca");
- **Bi-specific antibodies:** mosunetuzumab from Genentech/Roche, epcoritamab (previously known as GEN3013) from AbbVie/Genmab A/S, glofitamab (previously known as RG6026) from Genentech/Roche, odronextomab (previously known as REGN1979) from Regeneron, plamotamab (previously known as XmAb13676) from Xencor Inc. and magrolimab from Gilead Sciences, Inc.;
- **Antibody drug conjugates:** loncastuximab tesirine (previously known as ADCT-402) from ADC therapeutics, Adcetris® (brentuximab vedotin in CD30+ DLBCL) from Seagen Inc./Takeda and naratuximab emtansine (previously known as Debio1562) from DebioPharm;
- **Small molecules:** enzastaurin from Denovo Biopharma LLC, Calquence® (acalabrutinib) from Acerta Pharma, LLC/AstraZeneca, Venclexta® (venetoclax) from AbbVie/Genentech and Brukinsa™ (zanubrutinib) from Beigene, Ltd; and
- **Monoclonal antibodies:** umbralisib/ublituximab from TG Therapeutics Inc.

Endometrial Cancer

The initial treatment for endometrial cancer is surgery, radiotherapy and where applicable taxane/platinum-based chemotherapy. Upon disease progression, various chemotherapy agents are commonly used, and recently Keytruda® received U.S. and European approvals as a single agent or in combination with Lenvima® (lenvatinib, marketed by Esai) in a subgroup of patients with recurrent disease. Both Keytruda® and Lenvima® are also being evaluated in other endometrial cancer lines of therapy.

Other anti-cancer agents are in late-stage development for the treatment of patients with endometrial cancer, specifically for the use of "maintenance" therapy following initial treatment, as in the SIENDO Study and/or in recurrent disease, including:

- **Immune checkpoints inhibitors:** dostarlimab from GSK/Tesaro, Inc. ("Tesaro"), Tecentriq® (atezolizumab) from Genentech/Roche and Imfinzi® (durvalumab) from AstraZeneca; and
- **PARP inhibitor:** Lynparza® (olaparib) from AstraZeneca and Zejula® (niraparib) from GSK/Tesaro.

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 new medicine. 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 a number of years of experience in the biopharmaceutical industry in hematology/oncology. We have approximately 70 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 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 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.

We have long-term supply agreements with third-party contract manufacturers to manufacture clinical and commercial supplies of the drug product for XPOVIO and obtain all other supplies or materials for our other compounds on a purchase order basis. At this time, we rely on a single source supplier for our active pharmaceutical ingredient and drug product manufacturing requirements.

All of our products and product candidates are small molecules and are 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 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, 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.

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. The failure 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 an applicant and/or 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.

An applicant seeking approval to market and distribute a new drug product in the U.S. must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice ("GLP") regulations;
- 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 efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of an NDA;
- review of the product 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 facilities, methods and controls 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 and securing FDA approval of the NDA; 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 preclinical studies is subject to federal regulations and requirements, including GLP regulations. 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 continue after the IND is submitted.

In addition, companies 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 drug to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, 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. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

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 investigation 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 specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after 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.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain FDA regulatory requirements in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an IND application as support for an IND or an NDA. The final rule provides that such studies must be conducted in accordance with GCP, including review and approval by an independent ethics committee and informed consent from subjects. The GCP requirements in the final rule 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.

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 study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study 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 DSMB, 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 study. 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.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on its ClinicalTrials.gov website. Similar requirements for posting clinical trial information are present in the EU (EudraCT) website: https://eudract.ema.europa.eu/ and other countries, as well.

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.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

On December 13, 2016, the 21st Century Cures Act (the "Cures Act") established (and the 2017 Food and Drug Administration Reauthorization Act later amended) a requirement that sponsors of one or more investigational drugs for the treatment of a serious disease(s) or condition(s) make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug and biologic companies to make publicly available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 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 study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

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 study 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.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious AEs occur. 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 drug; and any clinically important increase in the case 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.

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

Submission of an NDA to the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2021 is $2,875,842 for an application requiring clinical data. The sponsor of an approved NDA is also subject to a program fee for fiscal year 2021 of $336,432. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA 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. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to certain performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it

determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. The FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain drug applications, including applications for drugs in a shortage or drugs for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential AEs, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use ("ETASU"). ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA may refer an application for a novel drug to an advisory committee or explain why such referral was not made. 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 recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

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

The FDA is authorized to designate certain products for expedited 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.

Specifically, the FDA may 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. 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, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. 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.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including 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-market studies or surveillance programs. After approval, many 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.

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 the U.S., healthcare professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. 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. 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, 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 the Prescription Drug Marketing Act ("PDMA") and its implementation regulations, as well as the Drug Supply Chain Security Act ("DSCSA"), which regulates the distribution of and tracing of prescription drugs and prescription drug samples at the federal level, and sets minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCSA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

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 applicant to rely, in part, on the FDA's previous findings of safety and efficacy 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 applicant for approval of the application "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. 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) applicant can establish that reliance on the FDA's

previous approval is scientifically appropriate, the applicant 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) applicant.

Abbreviated New Drug Applications for Generic Drugs

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, an applicant 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 Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity ("NCE") is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. 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, an ANDA 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 applicant 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 investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant 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 investigation 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

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant 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 applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant 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 applicant would.

Specifically, the applicant 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 applicant 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 applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant 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 applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant 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 applicant 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) applicant.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug 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. With enactment of the Food and Drug Administration Safety and Innovation Act ("FDASIA") in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted,

consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time. For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, FDA will meet early in the development process to discuss pediatric study plans with drug sponsors. The legislation requires FDA to meet with drug sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety days after FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, 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. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the U.S. and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. 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 patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which a generic (ANDA or 505(b)(2) NDA) applicant submitted a paragraph IV patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by a proposed generic product.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the U.S., or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the U.S. for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status 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 product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Orphan drug exclusivity will not bar approval of another orphan drug under certain circumstances, including if a subsequent product with the same drug for the same indication 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, or if the company with orphan drug exclusivity is not able to meet market demand. Legislation reverses prior precedent holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

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. We cannot provide any assurance that any patent term extension with respect to any U.S. patent will be obtained and, if obtained, the duration of such extension, in connection with any of our product candidates.

Review and Approval of Animal Drugs in the U.S.

In addition to pursuing approval of our product candidates for use in human beings, we may also seek approval of certain product candidates for veterinary applications. As with new drug products for human beings, new animal drugs may not be marketed in the U.S. until they have been approved by the FDA as safe and effective. The requirements and phases governing approval of a new animal drug are analogous to those for new human drugs. Specifically, the Center for Veterinary Medicine ("CVM") at FDA is responsible for determining whether a new veterinary product should be approved on the basis of a New Animal Drug Application ("NADA") filed by the applicant. A NADA must contain substantial evidence of the safety and effectiveness of the animal drug, as well as data and controls demonstrating that the product will be manufactured and studied in compliance with, among other things, applicable cGMP and GLP practices.

To begin this process, an applicant must file an Investigational New Animal Drug application ("INAD") with the CVM. The applicant will hold a pre-development meeting with the CVM to reach general agreement on the plans for providing the data necessary to fulfill requirements for a NADA. In this context, an applicant must submit pivotal protocols to the CVM for review and concurrence prior to conducting the required studies. The applicant will gather and submit data on safety, efficacy and chemistry, manufacturing and controls ("CMC") to the CVM for review, as below:

Safety: The design and review of the safety study and the study protocol are completed prior to initiation of the study to help assure that the data generated will meet FDA requirements. These studies are conducted under rigorous quality control, including GLP, to assure integrity of the data. They are designed to clearly define a safety margin, identify any potential safety concerns, and establish a safe dose for the product. This dose and effectiveness is then evaluated in the pivotal field efficacy study where the product is studied in the animal patient population in which the product is intended to be used.

Efficacy: Early pilot studies may be done in laboratory cats or dogs to establish effectiveness and the dose range for each product. When an effective dose is established, a study protocol to test the product in real world conditions is developed prior to beginning the study. The pivotal field efficacy study protocol is submitted for review and concurrence prior to study initiation, to help assure that the data generated will meet requirements. This study must be conducted with the formulation of the product that is intended to be commercialized, and is a multi-site, randomized, controlled study, generally with a placebo control.

CMC: To assure that the new animal drug product can be manufactured consistently, FDA will require applicants to provide documentation of the process by which the active ingredient is made and the controls applicable to that process that assure the active ingredient and the formulation of the final commercial product meet certain criteria, including purity and stability. After a product is approved, applicants will be required to communicate with FDA before any changes are made to these procedures or at the manufacturing site. Both the active ingredient and commercial formulations are required to be manufactured at facilities that practice cGMP.

Once all data have been submitted and reviewed for each technical section—safety, efficacy and CMC—the CVM will issue a technical section complete letter as each section review is completed. When the three letters have been issued, the applicant will compile a draft of the Freedom of Information Summary, the proposed labeling, and all other relevant information, and submit these as an administrative NADA for CVM review. Generally, if there are no deficiencies in the submission, the NADA will be issued within four to six months after submission of the administrative NADA. This review will be conducted according to timelines specified in the Animal Drug User Fee Act. The FDA's basis for approving a NADA is documented in a Freedom of Information Summary. Post-approval monitoring of products is required by law, with reports being provided to the CVM's Surveillance and Compliance group. Reports of product quality defects, AEs or unexpected results must also be produced in accordance with the relevant regulatory requirements.

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 efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing 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.

Procedures Governing Approval of Drug Products

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the EU has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of an EU member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial application must be accompanied by an investigational medicinal product dossier ("IMPD") with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

To obtain marketing approval of a product under EU regulatory systems, an applicant must submit an MAA either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the EC that is valid for all EU member states. 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.

Under the centralized procedure, the 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 applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants 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 applicant, known as the reference member state. Under this procedure, an applicant 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 reference member state and concerned member states. The reference member state 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 reference member state'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 EC, 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 applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a community authorization for the medicinal product is in the interest of patients at the community level.

Clinical Trial Approval

Requirements for the conduct of clinical trials in the EU including GCP are set forth in the Clinical Trials Directive 2001/20/EC and the GCP Directive 2005/28/EC. Pursuant to Directive 2001/20/EC and Directive 2005/28/EC, as amended, a system for the approval of clinical trials in the EU has been implemented through national legislation of the EU member states. Under this system, approval must be obtained from the competent national authority of each EU member state in which a study is planned to be conducted. To this end, a clinical trial application is submitted, which must be supported by an IMPD and further supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and other applicable guidance documents. Furthermore, a clinical trial may only be started after a competent ethics committee has issued a favorable opinion on the clinical trial application in that country.

In April 2014, the EU passed the new Clinical Trials Regulation, (EU) No 536/2014, which will replace the current Clinical Trials Directive 2001/20/EC. To ensure that the rules for clinical trials are identical throughout the EU, the new EU clinical trials legislation was passed as a regulation that is directly applicable in all EU member states. All clinical trials performed in the EU are required to be conducted in accordance with the Clinical Trials Directive 2001/20/EC until the new Clinical Trials Regulation (EU) No 536/2014 becomes applicable. The Clinical Trials Directive 2001/20/EC will, however, still apply three years from the date of entry into application of the Clinical Trials Regulation to (i) clinical trials applications submitted before the entry into application and (ii) clinical trials applications submitted within one year after the entry into application if the sponsor opts for old system.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the EU portal; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures that will spare sponsors from submitting broadly identical information separately to various bodies and different member states; a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts (Part I is assessed jointly by all member states concerned, and Part II is assessed separately by each member state concerned); strictly defined deadlines for the assessment of clinical trial applications; and the involvement of the ethics committees in the assessment procedure in accordance with the national law of the member state concerned but within the overall timelines defined by the Clinical Trials Regulation.

The Regulation was published on June 16, 2014 but has not yet become effective. As of January 1, 2020, the website of the EC reported that the implementation of the Clinical Trials Regulation was dependent on the development of a fully functional clinical trials portal and database, which would be confirmed by an independent audit, and that the new legislation would come into effect six months after the EC publishes a notice of this confirmation. The website indicated that the audit was expected to commence in December 2020. In late 2020, the EMA indicated that it plans to focus on the findings of a system audit; improving the usability, quality and stability of the clinical trial information system; and knowledge transfer to prepare users and their organizations for the new clinical trial system. The EMA has indicated that the system will go live in December 2021.

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

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 (“SMEs”) 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 Agency 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.

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 efficacy, 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 EC 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 drug on the EU market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid (the so-called sunset clause).

Data and Market Exclusivity

In the EU, NCEs qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which generic marketing authorizations can be submitted, and the innovator's data may be referenced, but not approved for two years. 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 sponsor is able to gain 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 database of pharmaceutical test, preclinical tests and clinical trials and obtain marketing approval of its product.

Orphan Drug Designation and Exclusivity

Regulation 141/2000 provides that a drug shall be designated as an orphan drug if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Community when the application is made, or that the product is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the European Community and that without incentives it is unlikely that the marketing of the drug in the European Community would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Community or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Regulation 847/2000 sets out criteria and procedures governing designation of orphan drugs in the EU. Specifically, 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. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. This period may, however, 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 drug designation, for example because the product is sufficiently profitable not to justify market exclusivity. Market exclusivity can be revoked only in very selected cases, such as consent from the marketing authorization holder, inability to supply sufficient quantities of the product, demonstration of "clinically relevant superiority" by a similar medicinal product, or, after a review by the Committee for Orphan Medicinal Products, requested by a member state in the fifth year of the marketing exclusivity period (if the designation criteria are believed to no longer apply). Medicinal products designated as orphan drugs pursuant to Regulation 141/2000 shall be eligible for incentives made available by the European Community and by the member states to support research into, and the development and availability of, orphan drugs.

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 promotion of medicinal products, interactions with clinicians, misleading and comparative advertising and unfair commercial practices. 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.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation ("GDPR"), which became effective on May 25, 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, 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.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the EU on January 31, 2020. Under the withdrawal agreement, there was a transitional period until December 31, 2020 (extendable by up to two years). On December 24, 2020, the United Kingdom and the EU entered into a Trade and Cooperation Agreement. The agreement sets out certain procedures for approval and recognition of medical products in each jurisdiction. Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom.

Furthermore, while the Data Protection Act of 2018 in the United Kingdom that "implements" and complements the GDPR, has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the European Economic Area ("EEA") to the United Kingdom will remain lawful under GDPR. The Trade and Cooperation Agreement provides for a transitional period during which the United Kingdom will be treated like an EU member state in relation to processing and transfers of personal data for four months from January 1, 2021. This may be extended by two further months. After such period, the United Kingdom will be a "third country" under the GDPR unless the EC adopts an adequacy decision with respect to transfers of personal data to the United Kingdom. The United Kingdom has already determined that it considers all of the EU 27 and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the United Kingdom to the EU/EEA remain unaffected.

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.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which third-party payors, including government health programs in the U.S. such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such products. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Payors also set other criteria to govern the uses of a drug that will be deemed medically appropriate and therefore reimbursed or otherwise covered. In particular, many public and private health care payors limit reimbursement and coverage to the uses of a drug that are either approved by the FDA or that are supported by other appropriate evidence (for example, published medical literature) and appear in a recognized drug compendium. Drug compendia are publications that summarize the available medical evidence for particular drug products and identify which uses of a drug are supported or not supported by the available evidence, whether or not such uses have been approved by the FDA. Nonetheless, product candidates may not be considered medically necessary or cost effective. Additionally, a payor’s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor’s determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In the U.S., we participate in, and have certain price reporting obligations to, the Medicaid Drug Rebate program, several state Medicaid supplemental rebate programs, and other governmental pricing programs. We also have obligations to report the average sales price for certain of our drugs to the Medicare program. Under the Medicaid Drug Rebate program, we are required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the states for our drugs under Medicaid.

Medicaid is a joint federal and state program that is administered by the states for low income and disabled beneficiaries. Medicaid rebates are based on pricing data reported by us on a monthly and quarterly basis to the Centers for Medicare & Medicaid Services ("CMS"), the federal agency that administers the Medicaid and Medicare programs. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug which, in general, represents the lowest price available from the manufacturer to any entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts, and other price concessions. The amount of the rebate is adjusted upward if average manufacture price increases more than inflation (measured by reference to the Consumer Price Index—Urban). If we become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are obligated to resubmit the corrected data for up to three years after those data originally were due, which revisions could affect our rebate liability for prior quarters.

Medicare is a federal program that is administered by the federal government that covers individuals age 65 and over or that are disabled as well as those with certain health conditions. Manufacturer-submitted information is used by CMS to calculate Medicare payment rates. Civil monetary penalties can be applied if we are found to have knowingly submitted any false pricing or other information to the government, if we are found to have made a misrepresentation in the reporting of our average sales price, or if we fail to submit the required data on a timely basis. Such conduct also could be grounds for CMS to terminate our Medicaid drug rebate agreement, in which case federal payments may not be available under Medicaid for our covered outpatient drugs.

Federal law requires that any company that participates in the Medicaid Drug Rebate program also participate in the Public Health Service's 340B drug pricing program (the "340B program") in order for federal funds to be available for the manufacturer's drugs under Medicaid. The 340B program, which is administered by the Health Resources and Services Administration ("HRSA") requires participating manufacturers to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. Covered entities include hospitals that serve a disproportionate share of financially needy patients, community health clinics, and other entities that receive certain types of grants under the Public Health Service Act. The 340B ceiling price is calculated using a statutory formula, which is based on the average manufacturer price and Medicaid rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate program. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. HRSA requires the federal ceiling price to be reported quarterly.

HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective on January 1, 2019. It is currently unclear how HRSA will apply its enforcement authority

under the new regulation. Any charge by HRSA that we have violated the requirements of the regulation could result in civil monetary penalties. HRSA also implemented a new price reporting system during the first quarter of 2019, under which manufacturers are now required to report their 340B ceiling prices to HRSA on a quarterly basis. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

Outside the U.S., ensuring adequate coverage and payment for our product candidates will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted regulatory approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Such restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal civil monetary penalty and false statement laws and regulations relating to pricing and submission of pricing information for government programs, including penalties for knowingly and intentionally overcharging 340B eligible entities and the submission of false or fraudulent pricing information to government entities;
- the federal Health Insurance Portability and Accountability Act of 1996 (“HIPAA”), as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (“HITECH”), which created additional federal criminal laws that prohibit, among other things, knowingly and willingly executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA and HITECH and their implementing regulations, which also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to CMS within the U.S. Department of Health and Human Services, information related to payments and other transfers of value to clinicians and teaching hospitals (and beginning in 2022, additional non-physician clinicians including physician assistants and nurse practitioners) and clinician ownership and investment interests; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

Some state laws 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 clinicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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 pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the U.S.

By way of example, the U.S. and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, Congress enacted the Patient Protection and Affordable Care Act ("ACA"), which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to our products and product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price" for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- the Independent Payment Advisory Board ("IPAB"), which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has been not been clearly defined. The ACA provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and

- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Other legislative changes have been proposed and adopted in the U.S. since the ACA 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. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments, will remain in effect through 2029 unless additional Congressional action is taken. The Coronavirus Aid, Relief, and Economic Security Act (the "CARES Act") and other COVID-19 relief legislation, suspended the 2% Medicare sequester from May 1, 2020 through March 3, 2021, and extended the sequester by one year, through 2030. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Since enactment of the ACA, there have been and continue to be numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by President Trump on December 22, 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. Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Further, the Bipartisan Budget Act of 2018, among other things, amended the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". The Congress will likely consider other legislation to replace elements of the ACA during the next Congressional session.

In addition, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the Court of Appeals for the Fifth Circuit affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. On January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis but subsequently agreed to hear the case on its regular calendar. On November 10, 2020, the Court heard oral argument. It is expected to issue a decision sometime this year. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce

coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

Further, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. For example, on May 11, 2018, the Trump Administration issued a plan to lower drug prices. In addition, the Trump Administration published a final rulemaking that allows states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants would be required to demonstrate that their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. At the same time, FDA issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products). In addition, President Trump issued five executive orders intended to lower the costs of prescription drug products. Several of these orders are reflected in recently promulgated regulations, and one of these regulations is currently subject to a nationwide preliminary injunction. It remains to be seen whether these orders and resulting regulations will remain in force during the Biden Administration.

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 health care authorities 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 health care 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 products or additional pricing pressures.

Human Capital Resources

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 towards the attraction, retention and development of personnel and the promotion and maintenance of diversity in our workforce. To support these objectives, our human resources programs reflect our commitment to our core values (Innovation, Courage, Urgency, Resiliency and Energy) and are designed to prioritize our employees' well-being, support their career goals, offer competitive wages and benefits, and enhance our culture through efforts aimed at making the workplace more satisfying, engaging and inclusive.

In order to attract, retain and reward our employees, we provide competitive compensation and benefits packages. We currently offer all new employees equity in the company and as incentive awards to all our employees in connection with our annual performance reviews. Our equity and cash incentive plans are aimed 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 and their objectives. In addition, many of our employees are stockholders of the 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 a 4% match for employee contributions 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. 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 and to help our employees cover medical expenses pre-tax, we also offer employees a Flexible Spending Account. Our employees outside the U.S. receive competitive compensation and benefits that are regularly benchmarked to ensure market norms and reflect our standards.

We encourage and support the growth and development of our employees and, wherever possible, seek to fill positions by promotion, transfer from within the organization and through our employee referral process. Continual learning and career development is advanced through ongoing performance and development conversations with employees, training programs, customized corporate training engagements and seminars and other training events employees are encouraged to attend in connection with their job duties.

Further, we strongly believe that diversity is a key driver of success. We strive to bring together employees with a wide variety of backgrounds, skills and culture and encourage all of our employees to maintain a work environment in which our differences are respected.

As of February 16, 2021, we had 432 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 corporate governance (“ESG”) positively impacting our social community and maintaining and cultivating good corporate governance. By focusing on such ESG policies and practices, we believe we can affect a meaningful and positive change in our community and maintain our open, collaborative corporate culture. Some of the initiatives that we were most proud of in 2020 included donating thousands of personal protection equipment items to hospitals, cancer centers, veterans organizations, and various community groups across the U.S. and around the globe in response to the COVID-19 pandemic. We were also proud to actively support a number of scholarship and mentoring programs for students in underserved communities as well as those interested in pursuing degrees in science and technology.

We look forward to continuing our commitment to giving back to our local communities in 2021 and beyond.

Information about our Executive Officers

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

Name	Age	Position
Michael G. Kauffman, M.D., Ph.D.	57	Chief Executive Officer and Director
Sharon Shacham, Ph.D., M.B.A.	50	President and Chief Scientific Officer
John Demaree	53	Chief Commercial Officer
Ran Frenkel, RPh.	52	Executive Vice President, Chief Development Officer
Tanya Lewis, M.S.	50	Executive Vice President, Chief Regulatory Affairs and Strategic Operations
Michael Mano	44	Senior Vice President, General Counsel and Secretary
Michael Mason	46	Senior Vice President, Chief Financial Officer and Treasurer
Stephen Mitchener	42	Senior Vice President, Chief Business Officer
Jatin Shah, M.D.	46	Executive Vice President, Chief Medical Officer

Michael G. Kauffman, M.D., Ph.D. Dr. Kauffman has served as Karyopharm's Chief Executive Officer since January 2011 and has been one of our directors since 2008. Dr. Kauffman co-founded Karyopharm with Dr. Sharon Shacham in 2008 and served as our President from 2011 to 2013 and as Chief Medical Officer from 2012 to 2013. Prior to joining Karyopharm, he was Chief Medical Officer of Onyx Pharmaceuticals Inc. ("Onyx"), a public biopharmaceutical company, from 2009 to 2010. From 2008 to 2009, Dr. Kauffman was Chief Medical Officer of Proteolix Inc., which was acquired by Onyx. At Proteolix, he led the development of Kyprolis® (carfilzomib), a novel proteasome inhibitor approved in refractory myeloma by the FDA in 2012. Dr. Kauffman was an operating partner at Bessemer Venture Partners from 2006 to 2008, where he led investments in biotechnology companies. From 2006 to 2008, he was President and Chief Executive Officer of Epix Pharmaceuticals, Inc. ("Epix"), a public biopharmaceutical company that underwent liquidation proceedings through an assignment for the benefit of creditors under Massachusetts law in 2009. Dr. Kauffman was President and Chief Executive Officer of Predix Pharmaceuticals, Inc. ("Predix"), a private biopharmaceutical company focused on G protein-coupled receptors, from 2002 until its merger into Epix in 2006. In that role, he led the merger of Predix and Epix, oversaw the discovery and development of four new clinical candidates and led collaboration transactions with Amgen and GlaxoSmithKline plc. From 2000 to 2002, Dr. Kauffman was Vice President, Clinical at Millennium Pharmaceuticals, Inc. ("Millennium"), a biopharmaceutical company, where he led the Velcade® development program. From 1997 to 2000, Dr. Kauffman held a number of senior positions at Millennium Predictive Medicine, Inc., a biopharmaceutical company and a subsidiary of Millennium, where he led the discovery and development of novel molecular diagnostics for major cancers, including melanoma and led transactions with Becton-Dickenson and Bristol Myers Squibb. From 1995 to 1997, Dr. Kauffman held a number of senior positions at Biogen Idec, Inc., a biopharmaceutical company, where he led the clinical development of anti-CD40L antibodies in autoimmune and inflammatory diseases, and acted as the main medical advisor to the Biogen business development group. Dr. Kauffman has served on the Board of Directors, the Audit Committee and as Chairman of the Compensation Committee of Kezar Life Sciences, Inc., a public biopharmaceutical company, since December 2016 and has been the lead director and a member of the Compensation Committee of Verastem Inc., a public biopharmaceutical company, since 2012. Dr. Kauffman previously served on the Board of Directors, Nominating and Governance Committee and Research and Development Committee of Infinity Pharmaceuticals, Inc., a public biopharmaceutical company, from April 2017 to March 2020. Dr. Kauffman received his B.A. in Biochemistry from Amherst College and his M.D. and Ph.D. from Johns Hopkins Medical School, and he trained in internal medicine and rheumatology at Beth Israel Hospital (now Beth Israel Deaconess Medical Center) and Massachusetts General Hospital. He is board certified in internal medicine.

Sharon Shacham, Ph.D., M.B.A. Dr. Shacham founded Karyopharm in 2008, has served as our Chief Scientific Officer since 2010 and as our President since 2013. Dr. Shacham served as our President of Research and Development from 2012 to 2013, as our Head of Research and Development from 2010 to 2012 and as our President and Chief Executive Officer from 2010 to 2011. Dr. Shacham established the company to focus on the discovery and development of small molecule inhibitors of nuclear export and has led our scientific progress since inception. Her computational drug discovery algorithms formed a critical part of the technological basis for our drug discovery and optimization expertise, which was used for the discovery of selinexor, our lead product. Dr. Shacham co-chairs our Scientific Advisory Board. Prior to founding Karyopharm, from 2006 to 2009, she was Senior Vice President of Drug Development at Epix, a biopharmaceutical company that underwent liquidation proceedings through an assignment for the benefit of creditors under Massachusetts law in 2009. She was Director, Algorithm and Software Development at Predix from 2000 until Predix's merger into Epix in 2006, where she led the company's efforts in GPCR modeling, computational chemistry, lead optimization and development of clinical trials. Dr. Shacham received her B.Sc. in Chemistry, Ph.D. and M.B.A. from Tel Aviv University.

John Demaree, M.B.A. Mr. Demaree has served as our Chief Commercial Officer since March 2020. Prior to joining Karyopharm, Mr. Demaree served as Chief Commercial Officer at G1 Therapeutics, Inc. ("G1"), a biopharmaceutical company, from July 2018 to March 2020 led its integrated commercial functions. Prior to G1, Mr. Demaree served as Vice President, Oncology Marketing at Astellas Pharma US, a pharmaceutical company, from July 2016 to July 2018 and as Executive Director from 2011 to July 2016, where he was responsible for establishing and leading the oncology marketing function, including the successful launch of XTANDI® (enzalutamide). Previously, Mr. Demaree led oncology business development and alliance management at Abbott Laboratories. He began his career serving in marketing leadership positions at Novartis and Eli Lilly. Mr. Demaree holds an M.B.A. in marketing and finance and a B.S. in marketing from Indiana University.

Ran Frenkel, RPh. Mr. Frenkel was appointed Executive Vice President, Worldwide Development Operations of Karyopharm in 2014, Executive Vice President, Chief Development Operations Officer from 2015 to August 2020 and EVP, Chief Development Officer in August 2020. Prior to joining Karyopharm, Mr. Frenkel held a number of senior management roles in Europe, Israel and the U.S., most recently as Managing Director EMEA from 2013 to 2014 for Clinipace Worldwide, an international clinical research organization, where he had responsibility for the overall management of the organization in Europe, the Middle East and Africa. Prior to becoming Managing Director EMEA, Mr. Frenkel was Vice President of International Business Development at Clinipace Worldwide from 2011 to 2013. Prior to joining Clinipace Worldwide, from 2007 to 2011, Mr. Frenkel established and managed the Israeli office of PFC Pharma Focus AG, which was acquired by Clinipace Worldwide in 2011, and from 2004 to 2007, he held the position of Managing Director at Actelion Pharmaceuticals with responsibility for all science and business affairs of the company in Israel. Mr. Frenkel received a BPharm from Hebrew University.

Tanya Lewis, M.S. Ms. Lewis joined Karyopharm in November 2018 as Senior Vice President, Regulatory and Quality Affairs and was appointed Executive Vice President, Chief Regulatory and Quality Officer in October 2019 and Executive Vice President, Chief Regulatory Affairs and Strategic Operations in October 2020. Prior to joining Karyopharm, Ms. Lewis held several leadership roles across the biopharmaceutical industry where she was instrumental in the successful negotiations for registration trial designs, approval, and/or commercialization of Velcade®, Varubi®, Integrilin® and Zejula®. Most recently Ms. Lewis served as Vice President, Regulatory and Quality Affairs for Syros Pharmaceuticals, Inc. ("Syros"), a pharmaceutical company, from January 2017 to July 2018. Prior to joining Syros, Ms. Lewis served as Vice President, Regulatory Affairs and Quality Assurance for Idera Pharmaceuticals, Inc. ("Idera"), a pharmaceutical company, from 2015 to December 2016. Prior to joining Idera, Ms. Lewis served as Vice President, Regulatory Affairs for Tesaro, Inc., a pharmaceutical company, from 2011 to 2015. Ms. Lewis has served on the board of directors of Replimune, Inc., a biotechnology company, since November 2020. Ms. Lewis holds a B.S. in Biology from Northeastern University and a M.S. in Regulatory Affairs and Public Health from Massachusetts College of Pharmacy and Allied Health Science.

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 Inc., a 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 January 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.

Michael Mason, C.P.A., M.B.A. Mr. Mason has served as our Senior Vice President, Chief Financial Officer and Treasurer since February 2019. Mr. Mason served as Vice President of Finance and Treasurer of Alnylam Pharmaceuticals, Inc., a public biopharmaceutical company, from 2011 until February 2019, as its Principal Accounting Officer from 2011 to October 2018, and as its Principal Financial Officer from 2011 to June 2016 and from January 2017 to May 2017. From 2005 to 2011, Mr. Mason served as Alnylam's Corporate Controller. From 2000 through 2005, Mr. Mason served in several finance and commercial roles at Praecis Pharmaceuticals Incorporated ("Praecis"), a public biotechnology company, most recently as Corporate Controller. Prior to Praecis, Mr. Mason worked in the audit practice at KPMG LLP, a national audit, tax and advisory services firm. Mr. Mason received a B.A. in Business Administration from Stetson University and an M.B.A. from Babson College and is a certified public accountant.

Stephen Mitchener, Pharm.D. Dr. Mitchener has served as our Chief Business Officer since December 2020. Prior to joining Karyopharm, Dr. Mitchener served as Chief Business Officer and Head, Strategic Finance from August 2019 to December 2020 and as Senior Vice President, Chief Business Officer from September 2018 to August 2019 at Axcella Health Inc. ("Axcella"), a biotechnology company. Before joining Axcella, Dr. Mitchener spent 15 years at Novartis, a pharmaceutical company, in roles of increasing responsibility, in both U.S. and international roles within its Oncology Business. He served as Head of Strategy, Partnering and Operations from July 2016 to August 2018 and as Oncology Franchise Head for Australia and New Zealand from 2013 to June 2016. During his tenure at Novartis, he also held various commercial, medical and business development roles, including Business Franchise Head, Oncology, Global Pharma Strategy Director, and Global New Product Director. Dr. Mitchener was involved in securing partnerships in oncology with multiple big pharma, technology, academic and healthcare partners. Dr. Mitchener received a PharmD from the University of North Carolina at Chapel Hill.

Jatin Shah, M.D. Dr. Shah joined Karyopharm in May 2017 as Vice President, Clinical Strategy, and was appointed Senior Vice President, Clinical Development in April 2018 and Executive Vice President, Chief Medical Officer in July 2019. Prior to joining Karyopharm, Dr. Shah held numerous roles at The University of Texas MD Anderson Cancer Center. From 2007 to August 2016, Dr. Shah served as an Assistant Professor, Associate Professor, and Associate Program Director of the Malignant Hematology Fellowship, as well as Director of Myeloma Clinical and Translational Research in the Department of Lymphoma/Myeloma, Division of Cancer Medicine. Dr. Shah received his M.D. from The Ohio State University College of Medicine, Columbus, Ohio and holds a degree in Mechanical Engineering from The Ohio State University. Dr. Shah completed his residency in internal medicine at the Cleveland Clinic Foundation, Cleveland, Ohio, and a fellowship in hematology/oncology at the University of Alabama at Birmingham. Dr. Shah holds board certification in hematology and oncology from the American Board of Internal Medicine.

Information about our Directors

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

Name	Age	Position
Michael G. Kauffman, M.D., Ph.D.	57	Chief Executive Officer of Karyopharm
Barry E. Greene	57	Chief Executive Officer of Sage Therapeutics, Inc., a biopharmaceutical company
Garen Bohlin	73	Former Executive Vice President of Constellation Pharmaceuticals, Inc., a biopharmaceutical company
Mikael Dolsten, M.D., Ph.D.	62	President of Worldwide Research, Development and Medical, Chief Scientific Officer and Executive Vice President of Pfizer Inc., a pharmaceutical company
Mansoor Raza Mirza, M.D.	59	Chief Oncologist at the Department of Oncology, Rigshopitalet – the Copenhagen University Hospital, Denmark and Medical Director of the Nordic Society of Gynaecological Oncology
Christy Oliger	51	Former Senior Vice President of the Oncology Business Unit at Genentech, Inc., a biotechnology company
Deepa R. Pakianathan, Ph.D.	56	Managing Member at Delphi Ventures, a venture capital firm focused on biotechnology and medical device investments
Richard Paulson.	53	Executive Vice President of Ipsen Pharmaceuticals, Inc., a biopharmaceutical company, and Chief Executive Officer of Ipsen North America
Chen Schor	48	President, Chief Executive Officer and Director of Adicet Bio, Inc., a biotechnology company

Available Information

Our Internet website is http://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 Committees of our Board of Directors are all available on our website at http://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. RiskFactors

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.

Risks Related to Commercialization and Product Development

Our business is substantially dependent on the commercial success of XPOVIO. If we are unable to successfully commercialize our current and future indications of XPOVIO or other products or product candidates on a timely basis, including our ability to achieve the 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 and other diseases in humans depend heavily on our 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 in the U.S. in multiple hematologic malignancy indications, including in combination with Velcade® (bortezomib) and dexamethasone for the treatment of patients with multiple myeloma after at least one prior therapy, in combination with dexamethasone for the treatment of patients with heavily pretreated multiple myeloma and as a monotherapy for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma ("DLBCL"). 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 successfully launch and achieve broad adoption of our approved products, such as the recently approved expanded XPOVIO indication based on the results from our Phase 3 BOSTON study or in any future indications for which XPOVIO may be approved, or any product candidates for which we obtain marketing approval;
- 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 or cost effectiveness;
- the competitive landscape for our products, including the timing of new competing products entering the market, such as BLENREP (belantamab mafodotin) and Monjuvi® (tafasitamab-cxix), which were both approved in 2020 and several new competing products expected to be approved in 2021, and the level and speed at which these products achieve market acceptance;
- the consistency of any new data we collect and analyses we conduct with prior results, whether they support a favorable safety, efficacy and effectiveness profile of XPOVIO and any potential impact on our U.S. Food and Drug Administration ("FDA") accelerated approval and/or FDA package insert for XPOVIO;
- our ability to comply with FDA 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, such as requirements in connection with the FDA's June 2020 approval of XPOVIO based on the results of the SADAL study to treat patients with DLBCL, which was approved under the FDA's Accelerated Approval Program;

- acceptance of current and future indications of XPOVIO and, if approved, our other product candidates, 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;
- 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 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;
- the effectiveness of our sales, marketing, manufacturing and distribution strategies and operations;
- 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;
- 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 requirements on physician prescribing practices and payor coverage; and
- the impact of the novel coronavirus disease ("COVID-19") pandemic on the above factors, including the limitation of our sales professionals to meet in person with healthcare professionals as the result of travel restrictions or limitations on access for non-patients.

If we do not achieve one or more of these factors in a timely manner, or at all, 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 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 are developing our product candidates. For example, BLENREP and Monjuvi® were approved by the FDA in August and July 2020, respectively. In addition, several new mechanism of actions may be introduced into the multiple myeloma market, including Car-T therapies, which may have a significant impact on the multiple myeloma 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 initially focused on developing and commercializing our current 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 may obtain approval for ours, which could result in our competitors establishing a stronger market position before we are able to enter the market or preventing us 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. If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of such product candidates.

Our long-term success depends in a large part on our ability to continue to successfully develop new indications of XPOVIO, our other product candidates or any new product candidates we may develop or acquire. Clinical testing is expensive, time consuming, difficult to design and implement, inherently uncertain as to outcome and can fail at any stage of testing. Furthermore, the failure of any product candidates to demonstrate safety and efficacy in any clinical trial could negatively impact the perception of XPOVIO 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.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to 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;
- 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 for the same indications as our product candidates;
- 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, or such requirements may not be as we anticipate;
- delays or failure in obtaining the necessary authorization from regulatory authorities or institutional review boards ("IRBs") to permit us 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;
- 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;
- 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 the ongoing COVID-19 pandemic, including impacts to healthcare systems and our trial sites' ability to conduct trials.

The COVID-19 pandemic may continue to have an impact on our clinical trials. At this time, however, we cannot fully forecast the scope of the impact that the COVID-19 pandemic may have on our ability to, among other things, initiate trial sites, enroll and assess patients, supply study drug and report trial results. In addition, we have and may continue to experience delays in the regulatory process as a result of the COVID-19 pandemic, which may impact our approval timelines, such as delays we encountered related to our reduced access to clinical trial sites in order to complete remonitoring activities associated with our Marketing Authorization Application ("MAA") for selinexor in multiple myeloma based on the results on the STORM study. Further, in response to the COVID-19 pandemic, the FDA issued guidance on March 18, 2020, and updated it on July 2, 2020 and January 27, 2021, to address the conduct of clinical trials during the pandemic. The guidance sets out a number

of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in the clinical study report (or as a separate document) contingency measures implemented to manage the study, and any disruption of the study as a result of COVID-19; a list of all study participants affected by COVID-19-related study disruptions by a unique subject identifier and by investigational site, and a description of how the individual's participation was altered; and analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, on a timely basis or at all, 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 may:

- not obtain marketing approval at all for the indication or product candidate;
- be delayed in obtaining marketing approval;
- 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, particularly as a result of the COVID-19 pandemic. 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.

Even if we or our collaborators complete the necessary preclinical studies and clinical trials for our product candidates, the marketing 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. 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. 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 of our other product candidates is safe and effective. If we are required to conduct additional clinical trials of selinexor or our 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. We have limited experience in conducting and managing the clinical trials necessary to obtain marketing approvals. 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 efficacy in accordance with regulatory agency standards based on a number of considerations, including adverse events ("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;
- 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 efficacy of our or our collaborators' product candidates to the satisfaction of regulatory agencies may be larger than we or they anticipated;
- the failure of clinical investigational sites and the records kept at such sites, including the 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 clinical trial sites, such as a March 2019 European Medicines Agency ("EMA") GCP inspection at our corporate headquarters and two clinical sites that participated in Part 2 of the STORM study, which resulted in certain findings that, although ultimately addressed, caused a delay in the approval process;
- regulatory authorities may change their approval policies or adopt new regulations;
- regulatory authorities may not be able to undertake reviews or approval processes in a timely manner, including delays as a result of the ongoing COVID-19 pandemic, such as with the EMA review of our MAA for selinexor in multiple myeloma based on the results of the STORM study and the resulting impact to the timing of our expected submission of an MAA for selinexor in multiple myeloma supported by the results of the BOSTON study or any future MAA;
- 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; 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.

Finally, disruptions at the FDA and other agencies may prolong the time necessary for new drugs 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, 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. The Trump Administration also took several executive actions that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities.

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.

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

We currently have four product candidates in clinical development for the treatment of human diseases: selinexor, eltanexor, verdinexor and KPT-9274. Their risk of failure is high. If our current or future indications of XPOVIO or any of our product candidates 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.

AEs in our clinical trials 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 XPOVIO were 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 were Grade 3 or Grade 4, meaning they were more than mild or moderate in severity, included 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 adverse events 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. We engage in training programs for medical personnel using selinexor to help them understand and manage the side effect profiles for our clinical trials and following commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of XPOVIO or our product candidates 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 and 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;
- regulatory authorities may require additional warnings on the label or impose distribution or use restrictions;
- patients and/or healthcare providers may elect to utilize other treatment options that have or are perceived to have more tolerable side effects;
- regulatory authorities may require one or more post-marketing studies;
- 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 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.

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.

The COVID-19 pandemic has adversely disrupted, and is expected to continue to adversely disrupt, our operations, including our clinical trial activities and commercial operations, which could have an adverse effect on our business and financial results.

As a result of the COVID-19 pandemic that has affected many segments of the global economy, we have experienced, and we expect to continue to experience, disruptions that could adversely impact our business, clinical trial activities and commercial operations, including:

- negative impact to revenue for XPOVIO, which may continue as the COVID-19 pandemic persists, including as a result of decreased new patient starts due to the inability of our sales force and our patients to meet with healthcare professionals;
- delays or difficulties in enrolling patients in our clinical trials, including our SIENDO and STOMP trials;
- delays or difficulties in initiating new clinical studies, including clinical site initiation and difficulties in recruiting clinical site investigators and clinical site staff;

- reduction or diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by government officials or entities, employers and others or interruption of clinical trial patient visits and study procedures (particularly any procedures that may be deemed non-essential), which may impact the integrity of clinical trial data and clinical study endpoints;
- interruption or delays in the operations of the FDA and comparable foreign regulatory agencies, including the EMA, which may impact regulatory review and approval timelines, such as the EMA review of our MAA for selinexor in multiple myeloma based on the results on the STORM study and any resulting impact to the timing of our expected submission of an MAA for selinexor in multiple myeloma supported by the results of the BOSTON study or any future MAA;
- negative impacts on any or all aspects of our operations due to business disruptions related to COVID-19 at our third-party vendors who we rely upon in the conduct of our business; and
- limitations on employee resources that would otherwise be focused on the conduct of our business, including because of sickness of employees or their families, the desire of employees to avoid contact with large groups of people, and an increased reliance on working from home.

The COVID-19 pandemic continues to evolve, and its ultimate scope, duration and effects remain unknown. The extent of the impact of the disruptions to our business, including commercial sales and clinical trials, as a result of the pandemic will depend on the availability and effectiveness of vaccines and therapeutics and future developments, which are highly uncertain and cannot be predicted with confidence, such as the duration and scope of the pandemic, and the effectiveness of actions taken in the U.S. and other countries to contain and treat the disease, such as travel restrictions, social distancing and quarantines or lock-downs in the U.S. and other countries, business closures or business disruptions.

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.

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. For example, certain data from our Phase 1 and Phase 2 clinical trials of selinexor are based on unaudited data provided by our clinical trial investigators. Finalization and cleaning of this data may change the conclusions drawn from this unaudited data provided by our clinical trial investigators indicating less promising results than we currently anticipate. 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, 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 example, in November 2020, we announced that our ongoing Phase 3 SIENDO study passed its planned interim futility analysis without the need to modify the study protocol or add additional patients. For this study or any other that we report preliminary, interim or top-line

data, we make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. Consequently, the preliminary, interim or top-line data results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. 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.

Further, even if our product candidates achieve their primary endpoints in Phase 3 clinical trials or other registration trials, the FDA or foreign regulatory authorities may disagree with our trial design or our interpretation of data from preclinical studies and clinical trials. If the FDA, or other regulatory authorities, disagree about the overall benefit-risk assessment and data analyses, we may decide not to pursue regulatory approval or we may not obtain approval for our product candidates, which could harm our business, financial condition, results of operations and prospects.

We expect that in any later phase clinical trial where patients are randomized to receive either selinexor on the one hand, or standard of care, supportive care or placebo on the other hand, the primary endpoint will be either progression-free survival, meaning the length of time on treatment until objective tumor progression, or overall survival, while the primary endpoint in any later phase clinical trial that is not similarly randomized may be different. In some instances, the FDA and other regulatory bodies have accepted overall response rate as a surrogate for a clinical benefit and have granted regulatory approvals based on this or other surrogate endpoints, such as in our SADAL study and our STORM study. These clinical trials were not randomized against control arms and the primary endpoints of these trials were overall response rate. If selinexor does not demonstrate sufficient overall response rates for any other indication for which a clinical trial has overall response rate as a primary endpoint, or if the FDA or foreign regulatory authorities do not deem overall response rate a sufficient endpoint, or deem a positive overall response rate to be insufficient, selinexor will likely not be approved for that indication based on the applicable study.

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

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. 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 other product candidates is approved for additional indications beyond hematological malignancies, such as solid tumors, we will need to substantially 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 intend to work with existing and potential partners to establish the commercial infrastructure to support a potential launch of selinexor outside of the U.S.

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. 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:

- 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
- existing or new competitors taking share from XPOVIO or preventing XPOVIO from gaining share in its approved indications.

Even if we or our collaborators are able to effectively commercialize XPOVIO or any product candidate 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 might obtain marketing approval for a drug in a particular country, but then be subject to price regulations that delay our 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 ability to successfully commercialize XPOVIO or any of our product candidates 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 by third-party payors. 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 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 obtain marketing approval. If reimbursement is not available or is available only at limited levels, we 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 regulatory authorities outside of the U.S. 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 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 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. will be 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 inflation, volatility in currency exchange rates or political instability in particular foreign economies and markets, including as a result of the current economic situation stemming from the COVID-19 pandemic;
- 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 pandemics (including the COVID-19 pandemic), geo-political actions, including war and terrorism, 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

We may seek approval from the FDA or comparable foreign regulatory authorities to use accelerated development pathways for our product candidates. If we are not able to use such pathways, we may be required to conduct additional clinical trials beyond those that we contemplate, which would increase the expense of obtaining, and delay the receipt of, necessary marketing approvals, if we receive them at all. In addition, even if an accelerated approval pathway is available to us, 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. Prior to seeking such accelerated approval, we will continue to seek feedback from the FDA or comparable foreign regulatory agencies and otherwise evaluate our ability to seek and receive such accelerated approval.

There can be no assurance that the FDA or foreign regulation agencies will agree with our surrogate endpoints or intermediate clinical endpoints in any of our clinical trials, or that we 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 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.

A failure to obtain 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.

Under accelerated or conditional approval regulations of the FDA or comparable foreign regulatory authorities, we must comply with post-approval development and regulatory requirements to maintain our approval of XPOVIO or any future approved products and, if we fail to do so, the FDA or comparable foreign regulatory authorities could withdraw its approval of XPOVIO or any future approved products for the indication that received accelerated or conditional approval, which would lead to substantially lower revenues.

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 (i) complete and submit a final report with full datasets from a randomized, double-blind, placebo-controlled Phase 3 trial that verifies and describes the clinical benefit of selinexor in patients with relapsed or refractory DLBCL and (ii) provide the interim and final analyses of a randomized Phase 2 clinical trial of selinexor to characterize the safety and efficacy of at least two different dosing regimens of selinexor monotherapy in patients with relapsed or refractory DLBCL after at least two prior lines of systemic therapy. We intend to satisfy the Phase 3 trial requirement though our recently initiated XPORT-DLBCL-030 study and we may not be able to successfully and timely complete this study or any other post-marketing confirmatory study as required to maintain approval or achieve full approval, including as a result of adverse impacts from the ongoing COVID-19 pandemic. If the required post-approval studies fail to verify the clinical benefits of XPOVIO or confirm that the surrogate marker used for accelerated approval of XPOVIO to treat DLBCL 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 would 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 have submitted or may submit to the EMA to support conditional approval of selinexor to treat heavily pretreated multiple myeloma, relapsed or refractory DLBCL, 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 in the European Union (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 finds that all four requirements are met: (i) the benefit-risk balance of the product is positive; (ii) it is likely that the applicant 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 need for further data. Once a conditional marketing authorization has been granted, the marketing authorization holder must fulfil 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.

If we are successful in obtaining a conditional marketing authorization for NEXPOVIO in the EU, this marketing authorization would be valid for a period for one year and could be renewed/prolonged if the conditions set out in the conditional marketing authorization are met. If we are not able to fulfill these specific obligations set out in the conditional marketing authorization requirements (which may include the presentation of additional clinical data on the safety and efficacy for NEXPOVIO), the marketing authorization for the EU may not be prolonged and we will no longer be able to market NEXPOVIO in the EU.

XPOVIO and any of our product candidates for which we or our collaborators obtain marketing approval in the future 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.

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 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 recordkeeping. For example, as a condition of the XPOVIO approval for the multiple myeloma and DLBCL indications, we are required to complete certain post-marketing commitments. 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 Risk Evaluation and Mitigation Strategy, which could include requirements for a restricted distribution system.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a drug. The FDA and other agencies, including the Department of Justice (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 do not market any of our product candidates for which we, or they, receive marketing approval for only their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing. Violation of the FDCA and 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. In addition, later discovery of previously unknown AEs or other problems with our products or their manufacturers or 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 must be ensured. These rules 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 European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU current Good Manufacturing Practice ("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.
- 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 2001/83EC, as amended, and are also subject to EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

If we or our collaborators do not comply with these and other applicable requirements, we or they may face enforcement actions by the European regulatory authorities that adversely affect our or their ability to market products in Europe and would have a material impact on our business.

Our or our collaborators' failure to obtain marketing approval in foreign jurisdictions would prevent our or their product candidates from being marketed abroad, and any approval we are granted for product candidates in the U.S. does not assure approval of product candidates in foreign jurisdictions.

In order to market and sell our products in the EU and many other jurisdictions, we and our current or future collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval outside of the U.S. may differ substantially from that required to obtain FDA approval. The marketing approval process outside of the U.S. generally includes at least all of the risks associated with obtaining FDA approval. In addition, 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. We and our collaborators may not obtain approvals from regulatory authorities outside of the U.S. on a timely basis, if at all. 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. 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.

In June 2016, the electorate in the United Kingdom ("UK") voted in favor of leaving the EU, commonly referred to as "Brexit". Following protracted negotiations, the UK left the EU on January 31, 2020 and the EU rules and regulations ceased to apply to the UK starting on January 1, 2021. In December 2020, the UK government and the EU agreed on a long-term trade agreement to govern economic relations going forward. Since the existing regulatory framework for pharmaceutical products in the UK is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime for pharmaceutical products in the UK, which remains uncertain. We and our collaborators are continuing to analyze how Brexit and the recently concluded trade agreement will affect the future regulatory regime for pharmaceutical products in the UK. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us or our collaborators from commercializing our product candidates in the UK and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we or our collaborators may be forced to restrict or delay efforts to seek regulatory approval in the UK and/or EU for our product candidates, which could significantly and materially harm our business.

Further, we expect that we or our collaborators will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the U.S., including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, or political instability in particular foreign economies and markets; compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the U.S.

We may seek certain designations for our product candidates, including Breakthrough Therapy, Fast Track and Priority Review designations, but we might not receive such designations, and even if we 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 request also seek a priority review designation for one or more of our product candidates. If the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, 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, 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. For example, in connection with our NDA for XPOVIO, in March 2019, the FDA extended the Prescription Drug User Fee Act action date by three months following our submission of additional, existing clinical information as an amendment to the NDA, which resulted in a nine-month review cycle despite the priority review designation. 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 or decide that the time period for FDA review or approval will not be shortened.

We may not be able to obtain orphan drug exclusivity for our product candidates.

Regulatory authorities in some jurisdictions, including the U.S. and Europe, may designate drugs and biologics for relatively small patient populations as orphan drugs. 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, which is generally defined as a patient population of fewer than 200,000 individuals annually in the U.S.

Generally, if a product 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 EMA or the FDA from approving another marketing application for the same product for that time period. The applicable period is seven years in the U.S. and ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may 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 patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity from the FDA for a product, as we have for XPOVIO as a treatment for patients with heavily pretreated multiple myeloma and DLBCL and selinexor in acute myeloid leukemia, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve a different product for the same condition if the FDA concludes 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.

Even if we or any of our collaborators obtain marketing approvals for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we, or they, manufacture and market our products, which could materially impair our ability to generate revenue.

Once marketing approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. We and our collaborators must therefore comply with requirements concerning advertising and promotion for XPOVIO or for any of our or their approved products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the drug's approved labeling. Thus, we and our collaborators may not be able to promote any product we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs, 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.

Accordingly, in connection with our currently approved products and assuming we or our current or future 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, regulatory authorities could withdraw the marketing approvals of our products, and 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.

Current and future legislation may increase the difficulty and cost for us and any collaborators to obtain marketing approval and commercialize our product candidates 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 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 "ACA"). In addition, other legislative changes have been proposed and adopted since the ACA 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 2030 under the Coronavirus Aid, Relief, and Economic Security Act (the "CARES Act"). 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. These 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.

Since enactment of the ACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by President Trump on December 22, 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. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the Court of Appeals for the Fifth Circuit court affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. Thereafter, the U.S. Supreme Court agreed to hear this case. Oral argument in the case took place on November 10, 2020, and a ruling by the Court is expected sometime this year. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

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 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.

Further, outside of the US, including the countries of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug. To obtain reimbursement or pricing approval in some countries, we or our existing and future collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our products to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

Current and future legislative efforts may limit the costs for our products, if and when they are approved for marketing, and that could materially impact our ability to generate revenues.

The containment of healthcare costs has become a priority of federal, state and foreign governments and the prices of pharmaceutical products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including rebate programs, price controls, restrictions on reimbursement and requirements for substitution of generic products. Controlling drug pricing has garnered bipartisan support in U.S. Congress. To that end, the Trump Administration published final rules that would allow states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants would be required to demonstrate their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. Earlier, the FDA had issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products). Further, President Trump issued five executive orders intended to lower the costs of prescription drug products. Several of these orders are reflected in recently promulgated regulations, and one of these regulations is currently subject to a nationwide preliminary injunction.

The Biden Administration has frozen certain of the previous administration's measures to reform drug prices, pending further review It remains to be seen how the Biden Administration will address this issue but, under Medicare Part D, the new administration may seek to establish a ceiling for the launch prices of all

branded, biologic, and certain generic drugs by referencing the *average* price of these drugs in other developed countries. At the same time, the administration may seek to limit Medicare Part D and public option drug prices through a tax penalty on manufacturers for increases in the cost of drugs and biologics above the general inflation rate. The Biden Administration may also seek to amend existing law that currently bans Medicare from negotiating lower prices with drug manufacturers.

At the state level, legislatures are increasingly 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 health care authorities 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 health care 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 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 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 may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

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.

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 the Centers for Medicare & Medicaid Services ("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 FSS 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 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.

Our relationships with healthcare providers and physicians and third-party payors are 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 providers, physicians and third-party payors play a primary role in the recommendation and prescription of our approved products. Our arrangements with third-party payors, healthcare providers and physicians 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 any approved product. These include the Federal Anti-Kickback Statute, the FCA and federal transparency requirements (and their state analogues), as discussed above in Item 1 under the heading "*Healthcare Law and Regulation*" in this Annual Report on Form 10-K.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not pre-empted by the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH"), thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations 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, imprisonment, exclusion of drugs 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 healthcare providers or entities with whom we do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the EU. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of EU Member States. Infringement of these laws could result in substantial fines and imprisonment.

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

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

We are subject to a significant number of privacy and data protection laws and regulations globally, many of which place restrictions on our ability to transfer, access and use personal data across our business. The legislative and regulatory landscape for privacy and data protection is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply, with additional laws and amendments being passed on a regular basis. For example, the EU General Data Protection Regulation (the "GDPR") imposes strict requirements on data controllers and processors of personal data, including personal health data, and penalties for noncompliance may include fines of up to four percent of a company's global annual revenue. The GDPR increases our obligations with respect to clinical trials conducted in the European Economic Area ("EEA") by expanding the definition of personal data to include coded data and requiring changes to informed consent practices and more detailed notices for clinical trial subjects and investigators. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside of the EU, including the U.S. and, as a result, increases the scrutiny that clinical trial sites located in the EEA should apply to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the U.S.

In the U.S., there are a broad variety of data protection laws that are applicable to our activities, and a wide range of enforcement agencies at both the state and federal levels that can review companies for privacy and data security concerns based on general consumer protection laws. For example, the California Consumer Privacy Act (the "CCPA"), which went into effect on January 1, 2020, creates similar risks and obligations as those created by GDPR, though the CCPA does exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects (the "Common Rule"). The California Privacy Rights Act, which took effect on January 1, 2021, significantly expands the CCPA. Many other states are considering similar legislation and a broad range of legislative measures also have been introduced at the federal level. In addition, the Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers.

Any inability to comply with applicable laws, regulations, policies, industry standards or other legal obligations regarding data protection or privacy either in the U.S. or in other jurisdictions where we do business could result in the imposition of fines, penalties, orders to stop non-compliant activities, or other liabilities, and could harm our reputation and our business.

Our employees, independent contractors, consultants and vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and 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 and vendors. Misconduct by these partners could include intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or 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 law, 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 misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to 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 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 any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates 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 recent 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.

On December 20, 2019, 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 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) applicant must take certain steps to request the reference product, which, in the case of products covered by a risk evaluation and mitigation strategy with elements to assure safe use, include obtaining authorization from the FDA for the acquisition of the reference product. If the applicant 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 applicant 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 new 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 other product candidates, if approved, which could impact our ability to maximize product revenue.

We are subject to governmental export and import controls that could impair our ability to compete in international markets due to licensing requirements and subject us to liability if we 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 fail to comply with these laws and regulations, we and certain of our 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 and 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.

Risks Related to Our Financial Position and Capital Requirements

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 $196.3 million for the year ended December 31, 2020. As of December 31, 2020, we had an accumulated deficit of $1.1 billion. 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 principally through private placements of

our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock, issuance of convertible debt, proceeds from a revenue interest financing agreement and cash generated from our 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 potentially outside of the U.S. and engage in activities to prepare for the potential approval and commercialization of additional indications for selinexor as well as our other product candidates. 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, 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 for XPOVIO and any of our other approved products from private and government payers within and outside of the U.S. and the impact of any pricing changes;
- initiating and successfully completing clinical trials required to file for, obtain and maintain U.S. and foreign 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;
- obtaining, maintaining and protecting our intellectual property rights; and
- navigating the negative impacts resulting from the ongoing COVID-19 pandemic to the healthcare systems, the ability of our clinical trial sites to conduct current or future trials and the regulatory review process.

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

- commercialize XPOVIO in the U.S., including maintaining or growing our commercial infrastructure;
- obtain and maintain regulatory approval for XPOVIO within and outside of the U.S., 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 conducted or are currently expected;
- maintain, expand and protect our intellectual property portfolio;
- manufacture XPOVIO and our product candidates;
- acquire or in-license other products, product candidates or technologies;

- add operational, financial and management information systems and personnel, including clinical, quality control, scientific, commercial and management personnel, to support our development and commercialization efforts and other operations required as a public company; and
- increase our insurance coverage as we grow our commercialization efforts.

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 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, including for the recently approved indication based on the BOSTON study, 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, 2020, we believe that our existing cash, cash equivalents and investments will enable us to fund our current operating and capital expenditure plans for at least twelve months from the date of issuance of the financial statements contained in this Annual Report on Form 10-K. 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 other product candidate that we develop or acquire, either within the U.S. or outside of the U.S.;
- 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;
- the extent to which we acquire or in-license other products, product candidates and technologies; and
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

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, any debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets. Our ability to satisfy and meet 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 our 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 the COVID-19 pandemic could negatively impact our ability to raise capital and we cannot predict the extent or duration of the macro-economic disruption stemming from the COVID-19 pandemic. 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 Revenue Interest Agreement with HCR contains various covenants and other provisions, which, if violated, could 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 XPOVIO.

In September 2019, we entered into the Revenue Interest Financing Agreement ("Revenue Interest Agreement") with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. ("HCR"). Pursuant to the 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 and limits on 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. In addition, the Revenue Interest Agreement 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 or specified revocations, or withdrawals or cancellations of regulatory approval for XPOVIO. Upon the occurrence of an event of default and in the event of a change of control, HCR may accelerate payments due under the Revenue Interest Agreement up to $138.8 million, less the aggregate of all of the payments previously paid to HCR. Upon the occurrence of specified material adverse events or the material breach of specified representations and warranties, which will not be considered events of default, HCR may elect to terminate the Revenue Interest Agreement and require us to make payments necessary for HCR to receive $75.0 million, less the aggregate of all of the payments made to date, plus a specified annual rate of return. In the event that we are unable to make such payment, then HCR may be able to foreclose on the collateral that was pledged to HCR, which consists of all of our present and future assets relating to XPOVIO. Any such foreclosure remedy would significantly and adversely affect us and could result in us losing our interest in such assets.

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 Convertible Senior Notes due 2025 (the "Notes").

We incurred $172.5 million of indebtedness as a result of the sale of the Notes and $75.0 million as a result of the initial closing pursuant to the Revenue Interest Agreement that we entered into with HCR in September 2019. We may also incur additional indebtedness to meet future financing needs. 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 Notes; and
- placing us at a possible competitive disadvantage with competitors that are less leveraged than us or have better access to capital.

Our ability to pay the principal of or interest on the Notes or to make cash payments in connection with any conversion of the Notes depends on our future performance, which is subject 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 Notes or other future indebtedness and make necessary capital expenditures. In addition, if the impact of the COVID-19 pandemic to our results of operations and business prospects is more severe and prolonged than we currently anticipate, our ability to repay the Notes could be impaired.

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

Holders may require us to repurchase their Notes following a fundamental change at a cash repurchase price generally equal to the principal amount of the Notes to be repurchased, plus accrued and unpaid interest. In addition, upon conversion, 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 the conversion in cash. If we do not have enough available cash at the time we are required to repurchase the Notes, pay cash amounts due upon conversion or redemption of the Notes or refinance the 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 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 Notes. In addition, our ability to repurchase the Notes, to pay cash upon conversion or redemption of the Notes or to refinance the Notes may be limited by law, regulatory authority or agreements governing any future indebtedness that we may incur. Our failure to repurchase the Notes at a time when the repurchase is required by the indenture governing the Notes or to pay cash upon conversion of the Notes as required by the indenture would constitute a default under the indenture. A default under the indenture or the fundamental change itself could also lead to a default under agreements governing our future indebtedness, if any. Moreover, the occurrence of a fundamental change under the indenture 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 Notes or to pay cash upon conversion of the Notes.

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

In the event the conditional conversion feature of the Notes is triggered, holders of Notes will be entitled to convert the Notes at any time during specified periods at their option. If one or more holders elect to convert their 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 Notes, we could be required under applicable accounting rules to reclassify all or a portion of the outstanding principal amount of the 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 that may be settled in cash, such as the Notes, could have a material effect on our reported financial results.

In May 2008, the Financial Accounting Standards Board ("FASB") issued FASB Staff Position No. APB 14-1, *Accounting for Convertible Debt Instruments That May Be Settled in Cash upon Conversion (Including Partial Cash Settlement)*, which has subsequently been codified as Accounting Standards Codification 470-20, *Debt with Conversion and Other Options* ("ASC 470-20"). Under ASC 470-20, an entity must separately account for the liability and equity components of the convertible debt instruments (such as the Notes) that may be settled entirely or partially in cash upon conversion in a manner that reflects the issuer's economic interest cost. The effect of ASC 470-20 on the accounting for the Notes is that the equity component is required to be included in the additional paid-in capital section of stockholders' equity at the issuance date, and the value of the equity component would be treated as debt discount for purposes of accounting for the debt component of the Notes. As a result, we will be required to record a greater amount of non-cash interest expense as a result of the amortization of the discounted carrying value of the Notes to their face amount over the term of the Notes. We will report a larger net loss in our financial results because ASC 470-20 will require interest to include both the amortization of the value of the debt discount and the instrument's coupon interest rate, which could adversely affect our future financial results, the market price of our common stock and the trading price of the Notes.

Effective January 1, 2021, we are adopting Accounting Standards Update No. 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging— Contracts in Entity's Own Equity (Subtopic 815-40)* that eliminates the requirement for the equity component to be bifurcated from the debt instrument and included in the additional paid-in capital section of stockholders' equity. Upon adoption, we will reclassify the equity component out of additional paid-in capital into the long-term liability. As a result, the equity component will no longer be treated as a debt discount for purposes of accounting for the debt, and non-cash interest expense related to amortizing the equity component will be eliminated in 2021 and beyond.

In addition, under certain circumstances, convertible debt instruments (such as the Notes) that may be settled entirely or partly in cash are currently eligible to be accounted for utilizing the treasury stock method, the effect of which is that the shares issuable upon conversion of the Notes are not included in the calculation of diluted earnings per share except to the extent that the conversion value of the Notes exceeds their principal amount. Under the treasury stock method, for diluted earnings per share purposes, the transaction is accounted for as if the number of shares of common stock that would be necessary to settle such excess, if we elected to settle such excess in shares, are issued. We cannot be sure that the accounting standards in the future will continue to permit the use of the treasury stock method. If we are unable to use the treasury stock method in accounting for the shares issuable upon conversion of the Notes, then our diluted earnings per share would be adversely affected.

Furthermore, if any of the conditions to the convertibility of the Notes is satisfied, then we may be required under applicable accounting standards to reclassify the liability carrying value of the Notes as a current, rather than a long-term, liability. This reclassification could be required even if no holders convert their Notes and could materially reduce our reported working capital.

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, 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. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. For example, during the term of the Revenue Interest Agreement, 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 HCR.

If we raise 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. For example, the COVID-19 pandemic has resulted in businesses suspending or terminating global operations and travel, self-imposed or government-mandated quarantines, and an overall slowdown of economic activity in many areas. 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 from the COVID-19 pandemic. 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. 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 from the COVID-19 pandemic, 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.

Our drug development programs and the commercialization of our products and product candidates, if approved, require 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 within and outside of the U.S. For example, we are parties to a license arrangement with Antengene 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. 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 SINE compounds for indications outside of oncology. For example, we expect to rely on partners to develop and commercialize our products outside of the U.S. 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 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 our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA 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. The 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 and document. 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 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.

Further, our ability to enter into new collaboration arrangements and the successful execution of our current arrangements by our collaborators could be negatively impacted by the COVID-19 pandemic, including as a result of businesses suspending or terminating global operations and travel, self-imposed or government-mandated quarantines, and a prolonged economic downturn. If our or our third-party collaborators are so affected, our business prospects and results of operations could be severely adversely impacted.

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 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 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, might cause delays or termination of the research, development or commercialization of 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;
- 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 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 supporting, or otherwise not effectively sell or support, XPOVIO;
- not devote the resources necessary to sell XPOVIO in the volumes and within the time frames 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 failing to meet deadlines for the completion of such trials, research or testing.

We rely on some 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 assure 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. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. 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, 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 product candidates 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.

In addition, as discussed above, the third-parties upon whom we rely to conduct our clinical trials could be negatively impacted as a result of disruptions caused by the COVID-19 pandemic, including difficulties in initiating clinical sites or enrolling participants, diversion of healthcare resources away from clinical trials, travel or quarantine policies, and other factors. If these third parties are so affected, our business prospects and results of operations could be severely adversely impacted.

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. We do not 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, including 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 an NDA 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 candidate 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.

We currently have long-term supply agreements with our third-party contract manufacturers to manufacture the clinical and commercial supplies of the drug product for XPOVIO. 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. Reliance on third-party manufacturers entails 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. For example, as a result of the COVID-19 pandemic, our suppliers and contract manufacturers could be disrupted by worker absenteeism, quarantines, or other travel or health-related restrictions or could incur increased costs

associated with ensuring the safety and health of their personnel. 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 may 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 in the U.S. and abroad related to our novel products and product candidates and other discoveries that are important to our business. As of February 2, 2021, 81 patents were in force that relate to XPO1 inhibitors, including composition of matter patents for selinexor, verdinexor and eltanexor in the U.S., and their use in targeted therapeutics. In addition, 17 patents were in force that relate to our PAK4/NAMPT inhibitors, including two composition of matter patents for KPT-9274 in the U.S. and its use 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 drugs, 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 drug 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 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 Drug Price Competition and Patent Term Restoration Act of 1984, referred to as 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 2, 2021, we have trademark registrations in the U.S. for our name and logo, and a combination of the two, XPOVIO, and PORE for our online portal. We also have pending applications in the U.S. to register two additional drug names (currently refused), and KARYFORWARD and a KARYFORWARD logo for our financial aid and charitable services. Outside 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. The KARYFORWARD logo is registered or pending in four jurisdictions outside 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 Employee Matters and Managing Growth

Our future success depends on our ability to retain our Chief Executive Officer, our President and Chief Scientific Officer and other key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on Michael Kauffman, M.D., Ph.D., our Chief Executive Officer, and Sharon Shacham, Ph.D., M.B.A., our President and Chief Scientific Officer, as well as the other principal members of our management and scientific teams. Although we have entered into formal employment agreements with Drs. Kauffman and Shacham and certain other 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.

Drs. Kauffman and Shacham are married to each other. The separation or divorce of the couple in the future could adversely affect our business.

Dr. Kauffman and Dr. Shacham are married to each other. As our Chief Executive Officer and our President and Chief Scientific Officer, respectively, they are a vital part of our operations. If they were to become separated or divorced or could otherwise not amicably work with each other, one or both of them may decide to cease his or her employment with us or it could negatively impact our working environment. Alternatively, their work performance may not be satisfactory if they become preoccupied with issues relating to their personal situation. In these cases, our business could be materially harmed.

We have expanded and expect to continue to expand our development, regulatory and sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We have experienced and expect to continue to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, clinical operations, regulatory affairs, sales, marketing and distribution. To manage our current and anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing such growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

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 from computer viruses, unauthorized access, 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 by malicious third parties. Cyber incidents are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. 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, 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.

If such an event 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. 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. 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.

If a material breach of our security or that of our vendors occurs, our financial or other confidential information could be compromised and could adversely affect our business or result in legal proceedings. In addition, the cost and operational consequences of implementing further data protection measures could be significant. 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, the possibility of these events occurring cannot be eliminated entirely.

Risks Related to Our Common Stock

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. Since February 16, 2020, our common stock price has ranged from $13.39 to $29.61. On February 16, 2021, the closing sale price of our common stock on The Nasdaq Global Select Market was $15.04 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 recent response to the ongoing COVID-19 pandemic and related world-wide economic disruptions. The market price for our common stock may be influenced by many factors, including:

- our 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, significant mergers, acquisitions, licenses, strategic collaborations or joint ventures;
- 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, 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 the ongoing COVID-19 pandemic;
- general economic, industry and market conditions;
- our ability to raise additional capital and the terms on which we can raise it;
- sales of large blocks of our common stock, including by our executive officers, directors and significant shareholders; and
- the other risks and uncertainties described in this “Risk Factors” section.

In addition, 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 been brought against a company following a decline 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 and we are therefore a target of this type of litigation. For example, we are currently subject to a securities class action litigation and a shareholder derivative lawsuit initiated against us and certain of our executive officers and directors and certain other defendants, as described further in Part I, Item 3, “*Legal Proceedings*” in this Annual Report on Form 10-K. We may face additional securities class action litigation or other litigation 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.

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 financial guidance relating to our expectations regarding our non-GAAP research and development and selling, general and administrative expenses, and expectations for our cash, cash equivalents and investments available for operations, which guidance is based on estimates and the judgment of management. If, for any reason, our expenses differ materially from our guidance or we utilize our cash more quickly than anticipated, 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, selinexor 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 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 shareholders 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. The TCJA significantly revises the Code. The TCJA, among other things, contains 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%, limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely), one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits.

As part of Congress' response to the COVID-19 pandemic, the Families First Coronavirus Response Act (the "FFCR Act") was enacted on March 18, 2020, the CARES Act was enacted on March 27, 2020, and COVID-19 relief provisions were included in the Consolidated Appropriations Act, 2021 ("CAA"), which was enacted on December 27, 2020. All contain numerous tax provisions. In particular, the CARES Act retroactively and temporarily (for taxable years beginning before January 1, 2021) suspends application of the 80%-of-income limitation on the use of net operating losses, which was enacted as part of the TCJA. It also provides that net operating losses arising in any taxable year beginning after December 31, 2017, and before January 1, 2021 are generally eligible to be carried back up to five years. The CARES Act also temporarily (for taxable years beginning in 2019 or 2020) relaxes the limitation of the tax deductibility for net interest expense by increasing the limitation from 30% to 50% of adjusted taxable income.

Regulatory guidance under the TCJA, the FFCR Act, the CARES Act, and the CAA is and continues to be forthcoming, and such guidance could ultimately increase or lessen their impact on our business and financial condition. It is also likely that Congress will enact additional legislation in connection with the COVID-19 pandemic, and as a result of the changes in the U.S. presidential administration and control of the U.S. Senate, additional tax legislation may also be enacted; any such additional legislation could have an impact on us. In addition, it is uncertain if and to what extent various states will conform to the TCJA, the FFCR Act, the CARES Act, or the CAA.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our headquarters are located in Newton, Massachusetts, where we lease 98,502 square feet of office and laboratory space. We also lease approximately 3,681 square feet of office space in Munich, Germany and 4,736 square feet of office space in Tel Aviv-Yafo, Israel.

Item 3. Legal Proceedings

The information required by this Item is provided under "Litigation" in Note 9 "*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 16, 2021, there were seven 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

None.

Item 6. Selected Financial Data

Not applicable.

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 titled "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 transport for the treatment of cancer and other diseases. 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 **S**elective **I**nhibitor of **N**uclear **E**xport ("SINE") compounds that inhibit the nuclear export protein exportin 1 ("XPO1"). These SINE compounds, representing 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, were the first oral XPO1 inhibitors to receive marketing approval. Our lead asset, XPOVIO® (selinexor), 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:

- 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 supported by data from the BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**on**e) study (the "BOSTON Study").
- 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 ("Pls"), at least two immunomodulatory agents ("IMiDs"), and an anti-CD38 monoclonal antibody. We refer to myeloma that is refractory to these five agents as penta-refractory. Approval in this indication was supported by data from the STORM (**S**elinexor **T**reatment of **R**efractory **M**yeloma) study (the "STORM Study").
- 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 supported by data from the SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study (the "SADAL Study"). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

The commercialization of XPOVIO, for both the multiple myeloma and DLBCL indications, is currently supported by sales representatives and nurse liaisons 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, healthcare providers and patients about XPOVIO's clinical profile and unique mechanism of action as we expand XPOVIO into the second-line plus multiple myeloma market and continue to penetrate the third-line DLBCL market.

XPOVIO also received its first regulatory approval outside the U.S. with an approval received in February 2021 by our partner Promedico Ltd., a member of the Neopharm Group ("Promedico"), for the treatment of patients with multiple myeloma and DLBCL, in Israel. In addition, in January 2021, the European Medicines Agency's ("EMA") Committee for Medicinal Products for Human Use adopted a positive opinion recommending the conditional approval of NEXPOVIO®(selinexor), the expected brand name for selinexor in Europe, based on

the results of the Phase 2b STORM Study, which studied selinexor in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two PIs, two IMiDs and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. We expect a final decision from the European Commission on our Marketing Authorization Application by April 2021. A favorable decision based on our submission through the centralized procedure would be valid in all 27 European Union member countries as well as the European Economic Area countries of Iceland, Liechtenstein and Norway. Further, we plan to submit a second regulatory filing to the EMA (Type II variation) by April 2021 based on the data from the Phase 3 BOSTON Study, which evaluated once-weekly NEXPOVIO in combination with once-weekly Velcade® and low-dose dexamethasone in patients with multiple myeloma after at least one prior therapy with the goal of further expanding the global reach of NEXPOVIO to additional patients in need of new treatment options.

Our focus is on marketing XPOVIO in its currently approved indications as well as seeking the regulatory approval and potential commercialization of selinexor as an oral agent in additional cancer indications with significant unmet medical need. We plan to continue to conduct clinical trials and 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. Thus, we are advancing our clinical development program for selinexor in the areas of multiple hematological malignancies and solid tumors, among others, including the following ongoing or planned selinexor studies:

- Phase 3 SIENDO (**S**elinexor/Placebo After Combination Chemotherapy **I**n Patients with Advanced or Recurrent **ENDO**metrial Cancer) study evaluating once weekly selinexor versus placebo as maintenance therapy in patients with endometrial cancer after first- or second-line chemotherapy (the "SIENDO Study");
- Phase 2/3 trial evaluating the combination of selinexor and R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) in patients with relapsed or refractory DLBCL. The Phase 3 portion of the study will evaluate the selected dose (as identified in the Phase 2 study) of selinexor or matching placebo given with the standard combination immunochemotherapy R-GDP to patients with at least one prior therapy and who are ineligible for high dose chemotherapy and cell-based intervention such as chimeric antigen receptor T-cell therapy (the "XPORT-DLBCL-030 Study");
- Phase 1b/2 STOMP (**S**elinexor and Backbone **T**reatments **o**f **M**ultiple Myeloma **P**atients) multi-arm study to evaluate combinations of selinexor with standard therapies in multiple myeloma (the "STOMP Study");
- Phase 1/2 study of selinexor in combination with standard of care therapy in patients with newly diagnosed or recurrent glioblastoma (the "XPORT-GBM-029 Study");
- Phase 1/2 study of selinexor in combination with ruxolitinib in treatment naïve patients with myelofibrosis ("MF") (the "XPORT-MF-034 Study");
- Phase 2 study of selinexor versus treatment per physician's choice in participants with previously treated MF (the "XPORT-MF-035 Study"); and
- Phase 1/2 study to assess the preliminary anti-tumor activity of selinexor in combination with docetaxel in patients with non-small cell lung cancer ("NSCLC") and with pembrolizumab in patients with colorectal cancer ("CRC") (the "XPORT-STP-027 Study").

Additionally, we expect to initiate a number of new clinical trials in 2021, including a Phase 3 study evaluating selinexor in combination with pomalidomide in patients with relapsed or refractory multiple myeloma as well as new Phase 1 and 2 studies evaluating selinexor in patients with a variety of solid tumor indications, including metastatic melanoma, lung cancer and colorectal cancer. A number of these studies will be investigating the treatment of selinexor in combination with other standard of care anti-cancer drugs.

In addition to selinexor, we are also advancing a pipeline of other novel product candidates including the following oral SINE compounds:

- **Eltanexor**: We are currently focusing on the development of eltanexor to treat patients with myelodysplastic syndrome as well as evaluating additional, potential solid tumor indications for future clinical development.
- **Verdinexor**: We are evaluating verdinexor as a potential therapy for viral, rare disease and autoimmune indications in humans, and our partner Anivive Life Sciences, Inc. ("Anivive") is evaluating verdinexor as a therapy for cancers in companion animals. In January 2021, Anivive received conditional approval from the FDA for LAVERDIA™-CA1 (verdinexor) as the first oral treatment of canine lymphoma.
- **KPT-9274:** We are evaluating KPT-9274, an oral inhibitor of p21-activated kinase 4 ("PAK4") and nicotinamide phosphoribosyltransferase ("NAMPT"), to treat patients with hematologic or solid tumors. In July 2020, the first patient was dosed in a Phase 1/2 clinical study of KPT-9274 in combination with an anti-PD1 monoclonal antibody.

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") to expand Antengene's development and commercial rights to our compounds in parts of Asia, Australia and New Zealand. We granted Antengene, our partner in China and other regions in Asia, the exclusive right to develop and commercialize selinexor and eltanexor in all human oncology indications in the following geographies comprising the Antengene Territory: China, Taiwan, Hong Kong, Macao, Brunei, South Korea, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, Vietnam, Australia and New Zealand. The Amended Antengene Agreement also includes the development and commercialization of KPT-9274 in all human oncology indications and verdinexor in human non-oncology indications in Australia and New Zealand. Under the terms of the Amended Antengene Agreement, we received a one-time upfront payment of $11.7 million from Antengene in June 2020. We are also eligible to receive additional payments if certain future prespecified development, regulatory and commercialization milestones are achieved by Antengene. In December 2020, we received $9.8 million in regulatory milestone payments from Antengene following certain regulatory filings by Antengene for selinexor in both multiple myeloma and DLBCL indications in Australia, Singapore and South Korea. In addition, 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. Certain countries in the Antengene Territory became available due to the reacquisition of exclusive development and commercial rights from Ono Pharmaceutical Co., Ltd. ("Ono") in April 2020.

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.

In addition, in February 2021, our partner Promedico Ltd, with whom we entered into an exclusive distribution agreement in February 2020 for the commercialization of XPOVIO in Israel and the Palestinian Authority, received a principal approval letter from the Israeli Ministry of Health granting approval of XPOVIO for the treatment of patients with either multiple myeloma or DLBCL in Israel.

As of December 31, 2020, we had an accumulated deficit of $1.1 billion. We had net losses of $196.3 million, $199.6 million and $178.4 million for the years ended December 31, 2020, 2019 and 2018, respectively. Net product sales for XPOVIO, which first became commercially available in the U.S. in July 2019, were $106.8 million from July 2019 through December 31, 2020. We anticipate that our expenses will continue to increase substantially as compared to prior periods as we continue to commercialize XPOVIO in the U.S. and

engage in activities to prepare for the potential commercialization of additional indications for selinexor and the potential approval of our other product candidates, including due to the impact of increased headcount, to support our clinical and commercialization activities and expanded infrastructure.

Critical Accounting Policies and 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. On an ongoing basis, we evaluate our estimates and judgments, including those described in greater detail below. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 "*Summary of Significant Accounting Policies"* to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K, we believe that the following accounting policies are the most critical to aid you in fully understanding and evaluating our financial condition and results of operations.

Revenue Recognition

We adopted Accounting Standards Update ("ASU") 2014-09, Revenue from Contracts with Customers, as well as subsequent amendments, which were codified in Financial Accounting Standards Board Accounting Standards Codification ("ASC") 606, on January 1, 2018, using the modified retrospective method for all contracts not completed as of the date of adoption. The adoption of ASC 606 did not have a material impact on our consolidated financial position, results of operations, stockholder's equity or cash flows as of the adoption date, as no transition adjustment for any of our contracts with customers was required.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements, and financial instruments. Under ASC 606, we recognize revenue when our customer obtains control of promised goods or services, in an amount that reflects the consideration which we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are within the scope of ASC 606, 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, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product Revenue Recognition

In the third quarter of 2019, we began to 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 to patients.

In connection with negotiating and executing contracts with our customers, our policy is to expense incremental costs of obtaining a contract when incurred, if the expected amortization period of the asset that we would have recognized is one year or less. However, no such costs have been incurred to date. In addition to distribution agreements with our customers, we 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.

In the context of ASC 606, 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, generally upon delivery pursuant to our agreements with our customers. If taxes should be collected from customers relating to product sales and remitted to governmental authorities, they will be 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 of the amounts noted are known at the time of sale based on contractual terms and, therefore, are recorded pursuant to the most likely amount method under ASC 606. Other amounts are estimated and take into consideration a range of possible outcomes, which are probability-weighted and recorded in accordance with the expected value method in ASC 606 for relevant factors, such as current contractual and statutory requirements, specific known market events and trends, industry data, and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the respective underlying contracts. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized under the contracts with our customers will not occur in a future period.

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, terms for which are explicitly stated in our contracts with such customers. We also pay fees for distribution services to our customers for sales order management, data, and distribution services, terms for 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 twelve months after the product's expiration date). We estimate the amount of product sales that will be returned using a probability-weighted estimate, initially calculated based on data from similar products and other qualitative considerations, such as visibility into the inventory remaining in the distribution channel. 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.

Based on the distribution model for XPOVIO, contractual inventory limits with our customers, the price of XPOVIO, and limited contractual return rights, we currently believe there will be minimal XPOVIO returns. However, we will 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. To date, we have determined a material reversal of revenue would not occur in a future period for the estimates detailed above, as of December 31, 2020 and, therefore, the transaction price was not reduced further during the year ended December 31, 2020. 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 and Asset Purchase Agreements

We generate revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain of our 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 customers may include non-refundable upfront fees, payments upon the exercise of customer options, payments based upon the achievement of defined milestones, and royalties on sales of product candidates if they are successfully approved and commercialized.

If a license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize the transaction price allocated to the license as revenue upon transfer of control of the license. We evaluate all other promised 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 is distinct. 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. If optional future services are priced in a manner which provides the customer with a significant or incremental discount, they are material rights, and are accounted for as performance obligations.

We utilize judgment to determine the transaction price. In connection therewith, we evaluate contingent milestones at contract inception to estimate the amount which is not probable of a material reversal to include 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 probable of being achieved until those approvals are received and therefore the variable consideration is constrained. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each reporting period, we re-evaluate the probability of achieving development milestone payments that may not be subject to a material reversal and, if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license and other revenue, as well as earnings, in the period of adjustment.

We then determine whether the performance obligations or combined 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 from non-refundable, upfront fees. 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 sales-based royalties, including sales-based milestone payments, and a license of intellectual property that is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of when the related sales occur or when the performance obligation to which some or all of the royalties have been allocated has been satisfied (or partially satisfied).

Accrued Research and Development Costs

As part of the process of preparing our consolidated financial statements, we estimate our accrued research and development costs. This process involves reviewing quotes and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service 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 paid to contract research organizations (“CROs”), and contract manufacturing organizations (“CMOs”), in connection with research and development activities for which we have not yet been invoiced.

We base our expenses related to CROs and CMOs on our estimates of the services received and efforts expended pursuant to quotes and contracts with 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 provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our 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. Our estimates have not been materially different than amounts actually incurred to date.

Results of Operations

The following table summarizes our results of operations:

	Years Ended December 31,		
	2020	2019	2018
	(in thousands)		
Product revenue, net	$ 76,210	$ 30,540	$ —
License and other revenue	31,875	10,353	30,336
Operating expenses:			
Cost of sales	2,705	2,407	—
Research and development	150,813	122,340	161,372
Selling, general and administrative	126,417	105,421	48,847
Loss from operations	(171,850)	(189,275)	(179,883)
Other (expense) income, net	(24,114)	(10,275)	1,502
Loss before income taxes	(195,964)	(199,550)	(178,381)
Income tax provision	(309)	(40)	(26)
Net loss	$(196,273)	$(199,590)	$(178,407)

Comparison of Years Ended December 31, 2020 and 2019

Product Revenue, net. We began generating product revenue from the sale of XPOVIO in the U.S. during the third quarter of 2019 following the July 2019 FDA approval of XPOVIO and its subsequent U.S. commercial launch. Net product revenue from U.S. commercial sales of XPOVIO for the year ended December 31, 2020 was $76.2 million compared to $30.5 million for the year ended December 31, 2019. In 2020, product revenue was negatively impacted by the COVID-19 pandemic as a result of reduced in-person access by our commercial team to physician customers and fewer patient visits as well as increased competition during 2020, specifically in the penta-refractory multiple myeloma setting.

We expect net product revenue to increase during 2021 as compared to 2020 following the expanded FDA approval of XPOVIO as a treatment for patients with multiple myeloma after at least one prior therapy in December 2020, however, we expect the COVID-19 challenges we experienced in 2020 to continue for at least the first part of 2021.

License and Other Revenue. License and other revenue for the year ended December 31, 2020 was $31.9 million compared to $10.4 million for the year ended December 31, 2019. We recognized $23.5 million in revenue pursuant to our license arrangement with Antengene, $5.0 million in revenue pursuant to a license arrangement with FORUS, $2.2 million upon reacquisition of the exclusive development and commercial rights from Ono and approximately $1.0 million in revenue for clinical supply provided to various partners, during the year ended December 31, 2020. In comparison, we recognized $9.4 million in revenue pursuant to our license arrangement with Antengene, $0.3 million in revenue for clinical supply provided to various partners, as well as $0.7 million in revenue pursuant to a government grant arrangement during the year ended December 31, 2019.

Cost of Sales. Cost of sales includes the cost of producing and distributing inventories that are related to U.S. XPOVIO product revenue during the respective period (including salary-related and stock-based compensation expenses for employees involved with XPOVIO production and distribution) and third-party royalties payable on our net product revenue for XPOVIO. We began capitalizing XPOVIO inventory costs during the third quarter of 2019 subsequent to FDA approval as it is our expectation that such costs will be recoverable through the commercialization of XPOVIO. Prior to the capitalization of XPOVIO inventory costs, such costs were recorded as research and development expenses in the period incurred. During the year ended December 31, 2020, we recorded $2.7 million of cost of sales, including $1.1 million related to royalties. During the year ended December 31, 2019, we recorded $2.4 million of costs of sales, including $1.6 million related to royalties. The cost of sales recorded during the years ended December 31, 2020 and 2019 only reflect a portion of the costs related to the manufacturing of XPOVIO and related materials, since, prior to FDA approval, these costs were expensed. The manufacturing costs of XPOVIO on-hand upon approval were approximately $2.8 million. At December 31, 2020, we had $2.2 million of this previously expensed XPOVIO and related material on-hand. We expect to utilize zero cost inventory with respect to XPOVIO for an extended period of time.

We expect cost of sales to increase during 2021 as compared to 2020 as a result of an expected increase in net product sales.

Research and Development Expense. Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with third parties, including 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 operating costs; and
- costs associated with preclinical activities and regulatory operations.

Costs for certain development activities, such as clinical trials, are recognized based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, and information provided to us by our vendors 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 reflected as prepaid expenses or accrued research and development expenses.

Since our research and development has been focused primarily on using our drug discovery and optimization platform to identify product candidates, we have not historically tracked research and development costs by project. In addition, we use our employee and infrastructure resources across multiple research and development projects. The majority of our research and development expenses to date have been related to selinexor.

Research and development expense increased by approximately $28.5 million to $150.8 million for the year ended December 31, 2020 from $122.3 million for the year ended December 31, 2019. The increase was primarily related to:

- an increase of $15.2 million in clinical trial costs, primarily related to COVID-19 trial activity as well as continued activity in our ongoing clinical trials;
- an increase of $13.6 million in personnel costs, primarily related to an increase in headcount; and

- an increase of $3.0 million in facility and IT infrastructure costs; partially offset by
- a decrease of $3.3 million in travel, consulting and professional costs.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect our research and development expenses to increase in 2021 as compared with 2020 as we continue clinical development of selinexor in our lead indications with a focus on regulatory submissions for selinexor. However, we do not believe that it is possible at this time to accurately project total program-specific expenses through commercialization. There are numerous factors associated with the successful commercialization of any of our product candidates, including future trial design and various regulatory requirements, many of which cannot be determined with accuracy at this time based on our stage of development. Additionally, future commercial and regulatory factors beyond our control could impact our clinical development programs and plans.

Selling, General and Administrative Expense. Selling, general and administrative expenses 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.

Selling, general and administrative expense increased by approximately $21.0 million to $126.4 million for the year ended December 31, 2020 from $105.4 million for the year ended December 31, 2019. The increase was primarily related to:

- an increase of $14.0 million in commercial-related activities, including two U.S. launches of XPOVIO during 2020;
- an increase of $12.0 million in personnel costs, primarily related to an increase in headcount; and
- an increase of $0.6 million in facility and IT infrastructure costs; partially offset by
- a decrease of $5.6 million in travel, consulting and professional costs.

We expect our selling, general and administrative expenses to increase in 2021 to support of our expanding operating and commercial activities related to sales and marketing of XPOVIO and any of our product candidates for which we obtain marketing approval.

Other (Expense) Income, Net. Other expense, net increased from $10.3 million for the year ended December 31, 2019 to $24.1 million for the year ended December 31, 2020. The increase of approximately $13.8 million was primarily due to an increase in interest expense of $11.5 million, increase in foreign currency translation losses of $0.2 million, coupled with a decrease in interest income of $2.6 million, offset by the realized gain resulting from the mark-to-market adjustment on our embedded derivative related to our deferred royalty obligation. $10.6 million of the increase in interest expense was related to our deferred royalty obligation and $0.9 million of the increase was attributable to our 3.00% convertible senior notes due 2025 (the “Notes”).

We expect interest expense to decrease in 2021, related to the adoption of ASU No. 2020-06, *Debt—Debt with Conversion and Other Options and Derivatives and Hedging—Contracts in Entity’s Own Equity*, on January 1, 2021. As a result of adoption, we expect non-cash interest expense associated with the amortization of our debt discount to be significantly reduced.

Results of Operations—Years Ended December 31, 2019 and 2018

Discussion and analysis of the year ended December 31, 2019 compared to the year ended December 31, 2018 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, 2019 as filed with the SEC on February 26, 2020 (“2019 Form 10-K”).

Liquidity and Capital Resources

Overview

During the third quarter of 2019, we began generating revenues from product sales, as XPOVIO first became commercially available in the U.S. in July 2019. While we began to generate revenue from the sales of XPOVIO in July 2019, to date, we have financed our operations through a combination of product revenue sales and through private placements of our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock, proceeds from the issuance of convertible debt, proceeds pursuant to the deferred royalty obligation, and cash generated from our business development activities.

As of December 31, 2020, our principal source of liquidity was $273.5 million of cash, cash equivalents and investments. We have had recurring losses and incurred a loss of $196.3 million for the year ended December 31, 2020. Net cash used in operations for the year ended December 31, 2020 was $160.2 million. We expect that cash, cash equivalents and investments at December 31, 2020 will be sufficient to fund our current operating plans and capital expenditure requirements for at least twelve months from the date of issuance of the financial statements contained in this Annual Report on Form 10-K.

Sources of Liquidity

On May 5, 2020, we entered into Amendment No. 1 to the Open Market Sale Agreement, dated August 17, 2018 (the "Open Market Sale Agreement"), with Jefferies LLC, as agent ("Jefferies"), pursuant to which we increased the maximum aggregate offering price of shares of our common stock that we may issue and sell from time to time through Jefferies, by $100.0 million from $75.0 million to up to $175.0 million. We did not sell any shares under the Open Market Sale Agreement during 2020. As of December 31, 2020, we have sold an aggregate of 3,712,359 shares under the Open Market Sale Agreement, for net proceeds of approximately $46.2 million, all of which were sold in 2019.

On March 6, 2020, we completed a follow-on offering under our shelf registration statement on Form S-3 pursuant to which we issued an aggregate of 7,187,500 shares of common stock, which included the full exercise of the underwriters' option to purchase additional shares, at a public offering price of $24.00 per share. We received aggregate net proceeds of approximately $161.8 million from the offering after deducting the underwriting discounts and commissions and other offering expenses.

On September 14, 2019, we entered into a deferred royalty obligation with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. ("HCR"). Pursuant to the deferred royalty obligation, HCR paid us $75.0 million, less certain transaction expenses, at the initial closing, which occurred on September 27, 2019, as disclosed in Note 15 "*Long-term Obligations"* to the Consolidated Financial Statements included under Part II, Item 8 of this Annual Report on Form 10-K.

On October 16, 2018, we completed an offering of $150.0 million aggregate principal amount of the Notes. In addition, on October 26, 2018, we issued an additional $22.5 million aggregate principal amount of the Notes pursuant to the full exercise of the option to purchase additional Notes granted to the initial purchasers in the offering. The Notes were sold in a private offering to qualified institutional buyers in reliance on Rule 144A under the Securities Act of 1933, as amended. The net proceeds from the sale of the Notes was $166.9 million, after deducting the initial purchasers' discounts and commissions and actual offering expenses payable by us.

On May 7, 2018, we completed a follow-on offering under our shelf registration statement on Form S-3 (File No. 333-222726) pursuant to which we issued an aggregate of 10,525,424 shares of common stock, which included the full exercise of the underwriters' option to purchase additional shares, at a public offering price of $14.75 per share. We received aggregate net proceeds of approximately $145.7 million from the offering after deducting the underwriting discounts and commissions and other offering expenses.

During the year ended December 31, 2020, we received $17.2 million in upfront payments under our license and distribution arrangements pursuant to which we are also entitled to receive 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. We did not receive upfront payments under license and distribution arrangements during the year ended December 31, 2019.

Cash flows

The following table provides information regarding our cash flows:

	Years Ended December 31,		
	2020	2019	2018
Net cash used in operating activities	$(160,234)	$(190,822)	$(159,117)
Net cash (used in) provided by investing activities	(53,685)	78,450	(107,664)
Net cash provided by financing activities	172,083	124,305	316,109
Effect of exchange rate changes	268	19	(78)
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (41,568)	$ 11,952	$ 49,250

Net Cash Used in Operating Activities

Net cash used in operating activities was $160.2 million during the year ended December 31, 2020 compared to $190.8 million during the year ended December 31, 2019. Net cash used in operating activities in both periods resulted primarily from our net losses adjusted for non-cash charges and changes in the components of working capital. The decrease in cash used in operating activities during the year ended December 31, 2020 compared to the year ended December 31, 2019 was driven by a $3.3 million decrease in our net loss due to increased revenues year over year and an increase of $12.6 million in non-cash charges and a $14.7 million increase in the components of working capital.

Net Cash (Used in) Provided by Investing Activities

Net cash used in investing activities was $53.7 million during the year ended December 31, 2020, and changed by approximately $132.1 million compared to $78.5 million in net cash provided by investing activities during the year ended December 31, 2019. The change was primarily related to a $96.1 million increase in the purchases of investments, coupled with a $36.1 million decrease in proceeds from the maturities of investments.

Net Cash Provided by Financing Activities

Net cash provided by financing activities was $172.1 million during the year ended December 31, 2020 compared to $124.3 million during the year ended December 31, 2019. The $47.8 million increase was primarily related to the net cash proceeds of $161.8 million from the sale of shares of our common stock from the follow-on offering under our shelf registration statement on Form S-3 during the first quarter of 2020, coupled with a $5.8 million increase in proceeds from the exercise of stock options and shares issued under our Employee Stock Purchase Plan in the year ended December 31, 2020 compared to the year ended December 31, 2019. This activity was partially offset by the $73.6 million in net proceeds received in the third quarter of 2019 from the execution of our deferred royalty obligation and the net proceeds of $46.2 million from the sale of shares of our common stock under the Open Market Sale Agreement during the year ended December 31, 2019.

A discussion of changes in our cash flow from the year ended December 31, 2018 to the year ended December 31, 2019 can be found in Part II, Item 7, "*Management's Discussion and Analysis of Financial Condition and Results of Operations*" of the 2019 Form 10-K.

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue to commercialize XPOVIO and continue the clinical trials of, and as we seek marketing approval for, our product candidates. In addition, we expect to incur significant commercialization expenses related to sales, marketing, manufacturing and distribution of any of our product candidates for which we obtain marketing approval, to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of any collaborator that we may have at such time for any such product candidate. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. 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.

We anticipate that we will continue to incur substantial expenses as we continue to commercialize XPOVIO in the U.S. and potentially outside of the U.S. and engage in activities to prepare for the potential approval and commercialization of additional indications for selinexor as well as our other product candidates. For a description of these expenses, please refer 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.

We expect that cash, cash equivalents and short- and long-term investments at December 31, 2020 will be sufficient to fund our current operating plans and capital expenditure requirements for at least twelve months from the date of issuance of the financial statements contained in this Annual Report on Form 10-K while we continue to commercialize XPOVIO in the U.S. and continue the clinical trials of our product candidates. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of current and planned drug discovery, preclinical development, laboratory testing and clinical trials for selinexor or our other product candidates;
- the amount and timing of revenue generated from commercial sales of XPOVIO;
- costs related to the sales and marketing of XPOVIO;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of future commercialization activities, including product sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval, to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of any collaborator that we may have at such time;
- our ability to establish and maintain collaborations on favorable terms, if at all;
- the success of any collaborations that we may enter into with third parties;
- the extent to which we acquire or in-license other products or technologies;
- the costs associated with legal activities, including litigation, arising in the course of business activities and our ability to prevail in any such legal disputes; and
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

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. While we began to generate revenue from the sales of XPOVIO in July 2019, 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. 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.

Off-Balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable Securities and Exchange Commission rules.

Inflation

We do not believe that inflation has had a significant impact on our revenues or results of operations since inception.

Recently Issued Accounting Pronouncements

Recent accounting pronouncements which may be applicable to us are described in Note 2 "*Summary of Significant Accounting Policies"* to our Consolidated Financial Statements included under Part II, Item 8 of this Annual Report on Form 10-K.

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 $273.5 million as of December 31, 2020. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because the majority of our investments are in short-term securities. 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 have an impact of approximately $1.0 million on the fair market value of our investment portfolio.

We do not believe our cash, cash equivalents, restricted cash 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 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

Our consolidated financial statements, together with the report of our independent registered public accounting firm, appears on pages 132 through 139 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 Chief Executive Officer) and principal financial officer (our Senior 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 Chief Executive Officer and Senior 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 Chief Executive Officer and Senior 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, 2020.

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, 2020.

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, 2020 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, 2020, 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, 2020, 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 2020 consolidated financial statements of the Company and our report dated February 24, 2021 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 24, 2021

Item 9B. Other Information

None.

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 2021 annual meeting of stockholders, pursuant to Regulation 14A of the Exchange Act, which we refer to as our 2021 Proxy Statement. We expect to file our 2021 Proxy Statement with the SEC within 120 days of December 31, 2020.

Item 10. Directors, Executive Officers and Corporate Governance

Information regarding our directors, including the audit committee and audit committee financial experts, and compliance with Section 16(a) of the Exchange Act, if applicable, will be included in our 2021 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 2021 Proxy Statement and 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 2021 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 2021 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 2021 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, 2020 and 2019, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2020, 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, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020, 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, 2020, 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 24, 2021 expressed an unqualified opinion thereon.

Adoption of ASU No. 2016-02

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, *Leases*, and related amendments.

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 $15.1 million at December 31, 2020. As discussed in Note 2 to the consolidated financial statements, the Company's accrued research and development costs are recognized based on various inputs, including an evaluation of the progress to complete specific tasks using data such as clinical site activations, patient enrollment, and other information provided to the Company by its service providers based on their actual costs incurred. Payments for these activities are based on the terms of individual arrangements, which may differ from the pattern of costs incurred, and are reflected on the consolidated balance sheet as accrued expenses.

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 third parties, 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 and estimates 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 24, 2021

Karyopharm Therapeutics Inc.
Consolidated Balance Sheets

(in thousands, except per share amounts)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 85,918	$ 128,858
Short-term investments	163,322	133,098
Accounts receivable	12,881	7,862
Inventory	2,644	346
Prepaid expenses and other current assets	9,285	7,289
Restricted cash	2,481	1,117
Total current assets	276,531	278,570
Property and equipment, net	2,219	3,046
Operating lease right-of-use assets	9,363	10,617
Long-term investments	24,215	2,016
Restricted cash	722	714
Total assets	$ 313,050	$ 294,963
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 4,450	$ 985
Accrued expenses	52,930	40,878
Deferred revenue	297	2,341
Operating lease liabilities	1,917	1,646
Other current liabilities	609	500
Total current liabilities	60,203	46,350
Convertible senior notes	117,928	109,857
Deferred royalty obligation	73,088	73,588
Operating lease liabilities, net of current portion	11,285	13,202
Deferred revenue, net of current portion	—	2,192
Total liabilities	262,504	245,189
Stockholders' equity:		
Preferred stock, $0.0001 par value; 5,000 shares authorized; none issued and outstanding	—	—
Common stock, $0.0001 par value; 200,000 shares authorized; 73,923 and 65,370 shares issued and outstanding at December 31, 2020 and December 31, 2019, respectively	7	7
Additional paid-in capital	1,119,632	923,142
Accumulated other comprehensive income (loss)	518	(37)
Accumulated deficit	(1,069,611)	(873,338)
Total stockholders' equity	50,546	49,774
Total liabilities and stockholders' equity	$ 313,050	$ 294,963

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, 2020	2019	2018
Revenues:			
Product revenue, net	$ 76,210	$ 30,540	$ —
License and other revenue	31,875	10,353	30,336
Total revenues	108,085	40,893	30,336
Operating expenses:			
Cost of sales	2,705	2,407	—
Research and development	150,813	122,340	161,372
Selling, general and administrative	126,417	105,421	48,847
Total operating expenses	279,935	230,168	210,219
Loss from operations	(171,850)	(189,275)	(179,883)
Other income (expense):			

Interest income	2,820	5,422	4,028
Interest expense	(27,140)	(15,647)	(2,493)
Other income (expense), net	206	(50)	(33)
Total other (expense) income, net	(24,114)	(10,275)	1,502
Loss before income taxes	(195,964)	(199,550)	(178,381)
Income tax provision	(309)	(40)	(26)
Net loss	$ (196,273)	$ (199,590)	$ (178,407)
Net loss per share—basic and diluted	$ (2.72)	$ (3.22)	$ (3.14)
Weighted-average number of common shares outstanding used to compute net loss per share—basic and diluted	72,044	61,955	56,780

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

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Karyopharm Therapeutics Inc.
Consolidated Statements of Comprehensive Loss

(in thousands)

	For the Years Ended December 31,		
	2020	2019	2018
Net loss	$ (196,273)	$ (199,590)	$ (178,407)
Comprehensive income (loss):			
Unrealized gains on investments	288	207	39
Foreign currency translation adjustments	267	—	(66)
Comprehensive loss	$ (195,718)	$ (199,383)	$ (178,434)

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

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Karyopharm Therapeutics Inc.
Consolidated Statements of Stockholders' Equity

(in thousands)

	Common Shares					
	Shares	Amount	Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2017	49,533	$ 5	$ 625,017	$ (217)	$ (495,341)	$ 129,464
Vesting of restricted stock	114	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	657	—	3,519	—	—	3,519
Stock-based compensation expense	—	—	17,275	—	—	17,275
Issuance of common stock, net of issuance costs	10,525	1	145,704	—	—	145,705
Equity component of convertible senior notes	—	—	67,850	—	—	67,850
Equity component of deferred financing costs for convertible senior notes	—	—	(2,209)	—	—	(2,209)
Unrealized gain on investments	—	—	—	39	—	39
Foreign currency translation adjustment	—	—	—	(66)	—	(66)
Net loss	—	—	—	—	(178,407)	(178,407)
Balance at December 31, 2018	60,829	6	857,156	(244)	(673,748)	183,170
Vesting of restricted stock	18	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	811	—	4,505	—	—	4,505
Stock-based compensation expense	—	—	15,291	—	—	15,291
Issuance of common stock, net of issuance costs	3,712	1	46,190	—	—	46,191
Unrealized gain on investments	—	—	—	207	—	207
Net loss	—	—	—	—	(199,590)	(199,590)
Balance at December 31, 2019	65,370	7	923,142	(37)	(873,338)	49,774
Vesting of restricted stock	204	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	1,161	—	10,307	—	—	10,307
Stock-based compensation expense	—	—	24,407	—	—	24,407
Issuance of common stock, net of issuance costs	7,188	—	161,776	—	—	161,776
Unrealized gain on investments	—	—	—	288	—	288
Foreign currency translation adjustment	—	—	—	267	—	267
Net loss	—	—	—	—	(196,273)	(196,273)
Balance at December 31, 2020	73,923	$ 7	$ 1,119,632	$ 518	$ (1,069,611)	$ 50,546

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

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Karyopharm Therapeutics Inc.
Consolidated Statements of Cash Flows

(in thousands)

	For the Year Ended December 31,		
	2020	2019	2018
Operating activities			
Net loss	$ (196,273)	$ (199,590)	$ (178,407)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	972	974	735
Net amortization of premiums and discounts on investments	1,419	(1,382)	29
Amortization of debt discount and issuance costs	8,071	7,193	1,420
Stock-based compensation expense	24,407	15,291	17,275
Realized and unrealized gain on marketable equity securities	(15)	—	—
Inventory obsolescence charge	329	—	—
Change in fair value of embedded derivative liability	(500)	—	—
Changes in operating assets and liabilities:			
Accounts receivable	(5,019)	(7,862)	—
Inventory	(2,627)	(346)	—
Prepaid expenses and other current assets	(1,996)	(868)	(4,663)
Operating lease right-of-use assets	1,254	1,094	—
Accounts payable	3,465	(3,301)	(1,380)
Accrued expenses and other liabilities	12,161	8,512	11,255
Deferred revenue	(4,236)	(9,362)	(8,027)
Deferred rent	—	—	2,646
Operating lease liabilities	(1,646)	(1,175)	—
Net cash used in operating activities	(160,234)	(190,822)	(159,117)
Investing activities			
Purchases of property and equipment	(145)	(206)	(2,363)
Proceeds from maturities of investments	221,037	257,145	137,510
Purchases of investments	(274,577)	(178,489)	(242,811)
Net cash (used in) provided by investing activities	(53,685)	78,450	(107,664)
Financing activities			
Proceeds from issuance of convertible senior notes, net of issuance costs	—	—	166,885
Proceeds from issuance of common stock, net of issuance costs	161,776	46,191	145,705
Proceeds from the exercise of stock options and shares issued under employee stock purchase plan	10,307	4,505	3,519
Proceeds from deferred royalty obligation, net	—	73,609	—
Net cash provided by financing activities	172,083	124,305	316,109
Effect of exchange rate on cash, cash equivalents and restricted cash	268	19	(78)
Net (decrease) increase in cash, cash equivalents and restricted cash	(41,568)	11,952	49,250
Cash, cash equivalents and restricted cash at beginning of period	130,689	118,737	69,487
Cash, cash equivalents and restricted cash at end of period	$ 89,121	$ 130,689	$ 118,737
Reconciliation of cash, cash equivalents and restricted cash reported within the consolidated balance sheets			
Cash and cash equivalents	$ 85,918	$ 128,858	$ 118,021
Short-term restricted cash	2,481	1,117	—
Long-term restricted cash	722	714	716
Total cash, cash equivalents and restricted cash	$ 89,121	$ 130,689	$ 118,737
Supplemental disclosures:			
Cash paid for interest on convertible debt	$ 5,175	$ 5,175	$ —
Operating lease right-of-use assets obtained in exchange for operating lease liabilities	$ —	$ 11,711	$ —
Cash paid for amounts included in the measurement of operating lease liabilities	$ 3,200	$ 2,889	$ —
Cash paid for interest on deferred royalty obligation	$ 6,014	$ —	$ —

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

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Karyopharm Therapeutics Inc.
Notes to Consolidated Financial Statements

1. Organization and Operations

The Company

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 and other diseases. Our **S**elective **I**nhibitor of **N**uclear **E**xport (**SINE**) compounds function by binding with and inhibiting the nuclear export protein exportin 1 ("XPO1"). Our initial focus has been on seeking the regulatory approval and commercialization of our lead SINE compound, selinexor, as an oral agent in cancer indications with significant unmet clinical need. We were incorporated in Delaware on December 22, 2008 and have a principal place of business in Newton, Massachusetts.

Our lead asset, XPOVIO® (selinexor), 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.

While we began to generate revenue from the sales of XPOVIO in July 2019, to date, we have financed our operations through a combination of product revenue sales and through private placements of our preferred stock, proceeds from our initial public offering and follow-on offerings of common stock, proceeds from the issuance of convertible debt, proceeds pursuant to a revenue interest financing agreement (deferred royalty obligation), and cash generated from our business development activities. As of December 31, 2020, we had an accumulated deficit of $1.1 billion. We expect to continue to incur significant expenses and we will need to continue to rely on additional financing to achieve our business objectives. We expect that our cash, cash equivalents and investments at December 31, 2020 will be sufficient to fund our current operating plans and capital expenditure requirements for at least twelve months from the date of issuance of these financial statements.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP").

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, in deciding how to allocate resources and in assessing performance. We view our operations and manage our business in one operating segment, which is the business of discovering, developing and commercializing drugs to treat cancer and certain other diseases. All of our revenue to date has been derived in the U.S. All of our material long-lived assets reside in the U.S.

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, clinical trial accruals, stock-based compensation expense, interest expense on our deferred royalty obligation and other reported amounts of expenses during the reported period. We base our estimates on historical experience and other market-specific or other 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.

Principles of Consolidation

The consolidated financial statements at December 31, 2020 include the accounts of (i) Karyopharm Therapeutics Inc., (ii) Karyopharm Securities Corp. ("KPSC", our wholly-owned Massachusetts corporation incorporated in December 2013), (iii) Karyopharm Europe GmbH (our wholly-owned German limited liability company, incorporated in September 2014), (iv) Karyopharm Therapeutics (Bermuda) Ltd. (our limited liability company, registered in Bermuda in March 2015), and (v) Karyopharm Israel Ltd. (our wholly-owned Israeli subsidiary formed in June 2018). All intercompany balances and transactions have been eliminated in consolidation.

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 in debt securities at the time of purchase. All of our securities are classified as available-for-sale and are reported as short-term investments or long-term investments based on maturity dates and whether such assets are reasonably expected to be realized in cash or sold or consumed during the normal cycle of business. Available-for-sale investments are recorded at fair value. Short-term and long-term investments are composed of corporate debt securities, commercial paper and U.S. government and agency securities. We review investments whenever the fair value of an investment is less than the amortized cost and evidence indicates that an investment's carrying amount is not recoverable within a reasonable period of time. 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, the present value of cash flows expected to be collected from the security is compared to the amortized cost basis of the security. If the present value of cash flows expected to be collected is less than the amortized cost basis, a credit loss exists and an allowance for a credit loss 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 available-for-sale security is confirmed or when either of the criteria regarding intent or requirement to sell is met.

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

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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, such as foreign currency exchange contracts, option contracts or other hedging arrangements.

Fair Value Measurements

Financial instruments, including cash, restricted cash, prepaid expenses and other current assets, accounts payable and accrued expenses, are presented at amounts that approximate fair value at December 31, 2020 and 2019.

We are required to 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 of the investments and is not a measure of the investment 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

Our cash equivalents are comprised of money market funds, U.S. government and agency securities, commercial paper and corporate debt securities. We measure these investments at fair value. The fair value of cash equivalents held in money market funds and U.S. government and agency securities is determined based on “Level 1” inputs.

Items classified as Level 2 within the valuation hierarchy consist of commercial paper, corporate debt securities, 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.

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 embedded derivative liability associated with our deferred royalty obligation is measured at fair value using an option pricing Monte Carlo simulation model and is included as a component of the deferred royalty obligation. The embedded derivative liability is subject to remeasurement at the end of each reporting period, with changes in fair value recognized as a component of other income (expense), net. The assumptions used in the option pricing Monte Carlo simulation model include: (i) our estimates of the probability and timing of related events; (ii) the probability-weighted net sales of XPOVIO and any of our other future products, including worldwide net product sales and upfront payments, milestone payments and royalties; (iii) our risk-adjusted discount rate that includes a company specific risk premium; (iv) our cost of debt; (v) volatility; and (vi) the probability of a change in control occurring during the term of the instrument. Our embedded derivative liability, as well as the estimated fair value of the deferred royalty obligation, is described in Note 15, “*Long-Term obligations*.”

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The following table presents information about our financial assets and liability that have been measured at fair value at December 31, 2020 and indicates the fair value hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

Description	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
Money market funds	$ 3,586	$ 3,586	$ —	$ —
U.S. government and agency securities	16,000	16,000	—	—
Commercial paper	8,999	—	8,999	—
Corporate debt securities	2,755	—	2,755	—
Investments:				
Short-term:				
Corporate debt securities	136,833	—	136,833	—
Commercial paper	23,487	—	23,487	—
U.S. government and agency securities	3,002	—	3,002	—
Long-term:				
Corporate debt securities (one to two-year maturity)	23,309	—	23,309	—

U.S. government and agency securities (one to two-year maturity)	906	—	906	—
	$ 218,877	$ 19,586	$ 199,291	$ —
Financial liability				
Embedded derivative liability	$ 1,800	$ —	$ —	$ 1,800

The following table presents information about our financial assets that have been measured at fair value at December 31, 2019 and indicates the fair value hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

Description	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
Money market funds	$ 71,380	$ 71,380	$ —	$ —
Investments:				
Short-term:				
Corporate debt securities	89,079	—	89,079	—
Commercial paper	39,022	—	39,022	—
U.S. government and agency securities	4,997	—	4,997	—
Long-term:				
Corporate debt securities (one to two-year maturity)	2,016	—	2,016	—
	$ 206,494	$ 71,380	$ 135,114	$ —
Financial liability				
Embedded derivative liability	$ 2,300	$ —	$ —	$ 2,300

The following table sets forth a summary of the changes in the estimated fair value of our embedded derivative liability during the year ended December 31, 2020 (in thousands):

	Embedded Derivative Liability
Balance as of December 31, 2019	$ 2,300
Change in fair value of derivative since issuance	(500)
Balance as of December 31, 2020	$ 1,800

Our Level 3 embedded derivative liability, as well as the estimated fair value of the deferred royalty obligation, is described in Note 15, "*Long-Term Obligations*".

Property and Equipment, Net

Property and equipment are recorded at cost, less accumulated depreciation and amortization. Depreciation 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 eliminated from the balance sheets and any related gains or losses are reflected in the consolidated statements of operations.

Leases

We adopted Accounting Standards Update ("ASU") 2016-02, *Leases (Topic 842)*, as well as subsequent amendments, which were codified in ASC 842, on January 1, 2019, using the optional transition method. Pursuant to the guidance under ASU 2016-02, we elected the optional package of practical expedients to leases that commenced prior to the effective date, which allowed us to not reassess: (i) whether expired or existing contracts contain leases; (ii) lease classification for any expired or existing leases; and (iii) initial direct costs for any existing leases. The new standard also allows entities to make certain policy elections, some of which we elected, including: (i) a policy to not record right-of-use assets and leases on the balance sheet for short-term leases that qualify and (ii) a policy to not separate lease and non-lease components for certain classes of underlying assets on contracts entered into or modified after the effective date. We did not elect the use of hindsight in estimating the lease term for leases subject to transition to the new standard.

The standard had a material impact on our consolidated balance sheet as of December 31, 2019, specifically through recognition of right-of-use assets of $11.7 million and lease liabilities of $16.0 million for our existing operating lease for office space in Newton, MA on the effective date. The difference between the operating lease right-of-use assets and operating lease liabilities is due to the change in classification of deferred rent and lease incentives through December 31, 2018 of $4.3 million from liabilities to a reduction in our operating lease right-of-use assets. The standard did not have a material impact on our consolidated statements of operations and comprehensive loss for the year ended December 31, 2019, as expense for our existing operating leases continues to be recognized consistent with the recognition pattern before adoption of the new standard.

At the inception of an arrangement, we determine if an arrangement is, or contains, a lease based on the unique facts and circumstances present in that arrangement. Lease classification, recognition, and measurement are then determined at the lease commencement date. For arrangements that contain a lease 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. 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. 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.

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 within our consolidated statements of operations.

Long-Lived Assets

We review the carrying values of our long-lived assets for possible impairment whenever events or changes in circumstances indicate that the carrying amounts of the assets may not be recoverable. Any long-lived assets held for disposal are reported at the lower of their carrying amounts or fair values less costs to sell. We have not recorded an impairment in any period since inception.

Accrued Research and Development Costs

As part of the process of preparing our consolidated financial statements, we estimate our accrued research and development costs. This process involves reviewing quotes and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service 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 paid to contract research organizations (“CROs”), and contract manufacturing organizations (“CMOs”), in connection with research and development activities for which we have not yet been invoiced.

We base our expenses related to CROs and CMOs on our estimates of the services received and efforts expended pursuant to quotes and contracts with 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 provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our 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. Our estimates have not been materially different than amounts actually incurred to date.

Revenue Recognition

We adopted ASU 2014-09, *Revenue from Contracts with Customers*, as well as subsequent amendments, which were codified in ASC 606, on January 1, 2018, using the modified retrospective method for all contracts not completed as of the date of adoption. The adoption of ASC 606 did not have a material impact on our consolidated financial position, results of operations, stockholder’s equity or cash flows as of the adoption date, as no transition adjustment for any of our contracts with customers was required.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements, and financial instruments. Under ASC 606, we recognize revenue when our customer obtains control of promised goods or services, in an amount that reflects the consideration which we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are within the scope of ASC 606, 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, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product Revenue Recognition

In the third quarter of 2019, we began to 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 to patients.

In connection with negotiating and executing contracts with our customers, our policy is to expense incremental costs of obtaining a contract when incurred, if the expected amortization period of the asset that we would have recognized is one year or less. However, no such costs have been incurred to date. In addition to distribution agreements with our customers, we 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.

In the context of ASC 606, 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, generally upon delivery pursuant to our agreements with our customers. If taxes should be collected from customers relating to product sales and remitted to governmental authorities, they will be 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 of the amounts noted are known at the time of sale based on contractual terms and, therefore, are recorded pursuant to the most likely amount method under ASC 606. Other amounts are estimated and take into consideration a range of possible outcomes, which are probability-weighted and recorded in accordance with the expected value method in ASC 606 for relevant factors, such as current contractual and statutory requirements, specific known market events and trends, industry data, and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the respective underlying contracts. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized under the contracts with our customers will not occur in a future period.

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, terms for which are explicitly stated in our contracts with such customers. We also pay fees

for distribution services to our customers for sales order management, data, and distribution services, terms for 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 twelve months after the product's expiration date). We estimate the amount of product sales that will be returned using a probability-weighted estimate, initially calculated based on data from similar products and other qualitative considerations, such as visibility into the inventory remaining in the distribution channel. 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.

Based on the distribution model for XPOVIO, contractual inventory limits with our customers, the price of XPOVIO, and limited contractual return rights, we currently believe there will be minimal XPOVIO returns. However, we will 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. To date, we have determined a material reversal of revenue would not occur in a future period, for the estimates detailed above, as of December 31, 2020 and, therefore, the transaction price was not reduced further during the year ended December 31, 2020. 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 and Asset Purchase Agreements

We generate revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain of our 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 customers may include non-refundable upfront fees, payments upon the exercise of customer options, payments based upon the achievement of defined milestones, and royalties on sales of product candidates if they are successfully approved and commercialized.

If a license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize the transaction price allocated to the license as revenue upon transfer of control of the license. We evaluate all other promised 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 is distinct. 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. If optional future services are priced in a manner which provides the customer with a significant or incremental discount, they are material rights, and are accounted for as performance obligations.

We utilize judgment to determine the transaction price. In connection therewith, we evaluate contingent milestones at contract inception to estimate the amount which is not probable of a material reversal to include 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 probable of being achieved until those approvals are received and therefore the variable consideration is constrained. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each reporting period, we re-evaluate the probability of achieving development milestone payments that may not be subject to a material reversal and, if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license and other revenue, as well as earnings, in the period of adjustment.

We then determine whether the performance obligations or combined 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 from non-refundable, upfront fees. 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 sales-based royalties, including sales-based milestone payments, and a license of intellectual property that is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of when the related sales occur or when the performance obligation to which some or all of the royalties have been allocated has been satisfied (or partially satisfied).

Accounts Receivable

In general, 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 30 days for specialty pharmacy customers and 65 days for specialty distributor customers. We analyze accounts for collectability, and periodically evaluate the creditworthiness of our customers. As of December 31, 2020 and 2019, respectively, we determined there were no credit losses associated with our accounts receivable based upon our review of contractual payment terms and individual customer circumstances, and therefore, an allowance for doubtful accounts was not required.

Inventory

Prior to regulatory approval, we expense costs relating to the production of inventory as research and development expense in the period incurred. We capitalize the costs to manufacture our products incurred after regulatory approval when, based on our judgment, future commercialization is considered probable and the future economic benefit is expected to be realized. Such costs are generally recorded as costs of sales upon shipment. In connection therewith, 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 material, 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.

Prior to FDA approval of XPOVIO, all costs related to the manufacturing of XPOVIO that could potentially be available to support the commercial launch of our products were charged to research and development expense in the period incurred, as there was no alternative future use. We analyze our inventory levels for recoverability each reporting period. In the period in which there is an impairment identified, we write down inventory that has become obsolete, inventory that has a cost basis in excess of its estimated realizable value, and inventory in excess of expected sales requirements as cost of sales. The determination of whether inventory costs will be realizable is based on our estimates. If actual market conditions are less favorable than we project, additional write-downs of inventory may be required, which would be recorded as cost of sales.

Cost of Sales

Cost of sales includes the cost of producing and distributing inventories that are related to product revenue during the respective period, including salaryrelated and stock-based 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. In addition, shipping and handling costs for product shipments are recorded in cost of sales as

incurred. Finally, cost of sales may also include costs related to excess or obsolete inventory adjustment charges, abnormal costs, unabsorbed manufacturing and overhead costs, and manufacturing variances.

Deferred Royalty Obligation

We treat the liability related to net revenues, as discussed further in Note 15, "*Long-term obligations"*, as a deferred royalty obligation, amortized under 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. In connection therewith, 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, with a corresponding impact to the reclassification 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.

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 contract research organizations, contract manufacturing organizations and consultants that help conduct clinical trials and preclinical studies;
- the cost of acquiring, developing and manufacturing clinical trial materials, including comparator drugs;
- facility, 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 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 the financial statements as prepaid or accrued research and development costs.

Comprehensive Loss

Comprehensive loss consists of net loss and changes in equity during a period from transactions and other equity and circumstances generated from non-owner sources, and currently consists of net loss, unrealized gains and losses on investments and foreign currency translation adjustments.

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 in the consolidated statements of operations. Net foreign exchange losses of $0.3 million were recorded in other income (expense), net for the year ended December 31, 2020. Net foreign exchange losses of less than $0.1 million were recorded in other income (expense), net for the years ended December 31, 2019 and 2018.

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 net 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 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 KPSC 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.

Accounting for Stock-Based Compensation

We account for our stock-based compensation awards in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments to employees and non-employees, including grants of employee stock options, restricted stock and restricted stock units, as well as modifications to existing stock options and shares issued under our employee stock purchase plan ("ESPP"), to be recognized in the consolidated statements of operations based on their fair values. We use the Black-Scholes option pricing model to determine the fair value of options granted.

Compensation expense related to awards to employees and non-employees with service based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the requisite service period of the award, which is generally the vesting term. Forfeitures are recognized as they occur.

Net Loss Per Share

Basic and diluted net loss per common share is calculated by dividing net loss by the weighted-average number of common shares outstanding for the period, without consideration for common stock equivalents. Our potential dilutive shares, stock options, unvested restricted stock and restricted stock units are considered to be common stock equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive.

The following potentially dilutive securities were excluded from the calculation of diluted net loss per share due to their anti-dilutive effect (in thousands):

	As of December 31,		
	2020	2019	2018
Outstanding stock options	11,276	9,843	8,917
Unvested restricted stock units	1,674	787	25

We have the option to settle the conversion obligation for our 3.00% convertible senior notes due 2025 (the "Notes") in cash, shares or any combination of the two. As the Notes were not convertible as of December 31, 2020, they were not participating securities and they did not have an impact on the calculation of basic earnings or loss per share. Based on our net loss position, there was no impact on the calculation of dilutive loss per share during the year ended December 31, 2020.

Recently Adopted Accounting Standards

In June 2016, the Financial Accounting Standards Board ("FASB") issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"). Certain amendments thereto were also issued by the FASB. ASU 2016-13 and the related amendments require that credit losses be reported as an allowance using an expected loss model, representing the

entity's current estimate of credit losses expected to be incurred. The previous accounting guidance, as applied by us through December 31, 2019, was based on an incurred loss model. For available-for-sale debt securities with unrealized losses, ASU 2016-13 and the related amendments now require allowances to be recorded instead of reducing the amortized cost of the investment. ASU 2016-13 and the related amendments were effective for interim and annual fiscal periods beginning after December 15, 2019. We adopted this guidance effective January 1, 2020. The adoption of this standard did not have a material impact on our consolidated financial statements.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement—Disclosure Framework-Changes to the Disclosure Requirement for Fair Value Measurement* ("ASU 2018-13"). The amendments in ASU 2018-13 modify the disclosure requirements on fair value measurements in Accounting Standards Codification ("ASC") 820, *Fair Value Measurement*, based on the concepts in the FASB Concepts Statement, including the consideration of costs and benefits. The amendments under ASU 2018-13 were effective for interim and annual fiscal periods beginning after December 15, 2019, with early adoption permitted. We adopted this guidance effective January 1, 2020. The adoption of this standard did not have a material impact on our consolidated financial statements.

Recently Issued Accounting Standards

In August 2020, the FASB issued ASU No. 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40)* ("ASU 2020-06"). ASU 2020-06 reduces complexity of accounting for convertible debt and other equity-linked instruments. The new standard is effective for companies that are SEC filers (excluding smaller reporting companies) for fiscal years beginning after December 15, 2021 and interim periods within that year, and two years later for other companies. Companies can early adopt the standard at the start of a fiscal year beginning after December 15, 2020. The standard can either be adopted on a modified retrospective or a full retrospective basis. We plan to early adopt the standard on January 1, 2021 using the modified retrospective basis. Upon adoption of ASC 2020-06, we expect the carrying value of our convertible debt will increase by approximately $50.6 million with a corresponding decrease to additional paid-in capital of $65.6 million and a decrease to accumulated deficit of $15.0 million. Our deferred tax liability is also expected to decrease by approximately $11.8 million with a corresponding increase in the income tax valuation allowance. While we do not expect a material impact to our consolidated statements of operations and consolidated statements of cash flows upon adoption, non-cash interest expense associated with the amortization of debt discounts will be significantly reduced in future periods.

CARES Act

In March 2020, the Coronavirus Aid, Relief, and Economic Security ("CARES") Act was signed into law and provides an estimated $2.2 trillion to fight the COVID-19 pandemic and stimulate the U.S. economy. The business tax provisions of the CARES Act include temporary changes to income and non-income-based tax laws. Some of the key income tax provisions include (i) eliminating 80% of taxable income limitations by allowing corporate entities to fully utilize net operating loss ("NOL") carryforwards to offset taxable income in 2020, 2019 or 2018 and reinstating it for tax years after 2020; (ii) allowing NOLs generated in 2020, 2019 or 2018 to be carried back five years; (iii) increasing the net interest expense deduction limit to 50% of adjusted taxable income from 30% for the 2020 and 2019 tax years; (iv) allowing taxpayers with alternative minimum tax credits to claim a refund for the entire amount of the credit instead of recovering the credit through refunds over a period of years, as required by the 2017 Tax Cut and Jobs Act; and (v) allowing entities to deduct more of their charitable cash contributions made during calendar year 2020 by increasing the taxable income limitation to 25% from 10%. Companies are required to account for these provisions in the period that includes the March 2020 enactment date (i.e., the first quarter for calendar year-end entities). We have assessed the impact of these provisions and they are not material to our consolidated financial statements or related disclosures.

Measures not related to income-based taxes within the CARES Act include (i) allowing an employer to pay its share of Social Security payroll taxes that would otherwise be due from the date of enactment through December 31, 2020 over the following two years and (ii) allowing eligible employers subject to closure due to the COVID-19 pandemic to receive a 50% credit on qualified wages against their employment taxes each quarter, with any excess credits eligible for refunds. These measures of the CARES Act also are not material to our consolidated financial statements or related disclosures.

3. Property and Equipment, Net

Property and equipment, net consisted of the following (in thousands):

	Estimated Useful Life (In Years)	December 31, 2020	December 31, 2019
Laboratory equipment	4	$ 610	$ 593
Furniture and fixtures	5	654	654
Office and computer equipment	3	702	598
Leasehold improvements	Lesser of useful life or lease term	5,441	5,443
		7,407	7,288
Less accumulated depreciation and amortization		(5,188)	(4,242)
		$ 2,219	$ 3,046

Depreciation and amortization expense recorded for the years ended December 31, 2020, 2019, and 2018 was $1.0 million, $1.0 million and $0.7 million, respectively.

4. Investments

The following table summarizes our investments in debt securities, classified as available-for-sale as of December 31, 2020 (in thousands):

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Loss	Fair Value
Short-term:				
Corporate debt securities	$ 136,677	$ 189	$ (33)	$ 136,833
Commercial paper	23,485	3	(1)	23,487
U.S. government and agency securities	3,002	—	—	3,002
Long-term:				
Corporate debt securities (one to two-year maturity)	23,195	126	(12)	23,309
U.S. government and agency securities (one to two-year maturity)	897	9	—	906
	$ 187,256	$ 327	$ (46)	$ 187,537

The following table summarizes our investments in debt securities, classified as available-for-sale as of December 31, 2019 (in thousands):

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Loss	Fair Value
Short-term:				
Corporate debt securities	$ 89,110	$ 12	$ (43)	$ 89,079
Commercial paper	39,004	18	—	39,022
U.S. government and agency securities	4,990	7	—	4,997
Long-term:				
Corporate debt securities (one to two-year maturity)	2,017	—	(1)	2,016
	$ 135,121	$ 37	$ (44)	$ 135,114

At December 31, 2020 and 2019, we held 37 and 27 debt securities, respectively, that were in an unrealized loss position. The unrealized losses at December 31, 2020 and 2019 are attributable to changes in interest rates and we do not believe any unrealized losses represent credit losses. We do not intend to sell these securities and it is not more likely than not that we will be required to sell them before recovery of their amortized cost basis. The following table summarizes our debt securities in an unrealized loss position for which an allowance for credit losses has not been recorded at December 31, 2020, aggregated by major security type and length of time in a continuous unrealized loss position (in thousands):

	Less than 12 Months		12 Months or Longer		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Commercial paper	$ 2,496	$ (1)	$ —	$ —	$ 2,496	$ (1)
Corporate debt securities	85,984	(45)	—	—	85,984	(45)
Total	$ 88,480	$ (46)	$ —	$ —	$ 88,480	$ (46)

The following table summarizes our debt securities in an unrealized loss position for which an allowance for credit losses has not been recorded at December 31, 2019, aggregated by major security type and length of time in a continuous unrealized loss position (in thousands):

	Less than 12 Months		12 Months or Longer		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Corporate debt securities	$ 63,845	$ (44)	$ —	$ —	$ 63,845	$ (44)
Total	$ 63,845	$ (44)	$ —	$ —	$ 63,845	$ (44)

5. Inventory

The following table presents our inventory of XPOVIO (in thousands):

	December 31,	
	2020	2019
Raw materials	$1,919	$—
Work in process	646	273
Finished goods	79	73
Total inventory	$2,644	$346

At December 31, 2020 and 2019, all of our inventory was related to XPOVIO, which was approved by the FDA in July 2019, at which time we began to capitalize costs to manufacture XPOVIO. Prior to FDA approval of XPOVIO, all costs related to the manufacturing of XPOVIO and related material were charged to research and development expense in the period incurred. During 2020, we recorded an inventory-related excess and obsolescence provision of $0.3 million. We did not record such a provision in 2019.

6. Accrued Expenses

Accrued expenses consisted of the following (in thousands):

	December 31,	
	2020	2019
Payroll and employee-related costs	$ 16,214	$ 13,630
Research and development costs	15,087	13,122
Interest	12,250	4,371
Professional fees	5,229	6,172
Other	4,150	3,583
	$ 52,930	$ 40,878

7. Related Party Transactions

We paid consulting expenses of $0.3 million, $0.2 million and $0.2 million for the years ended December 31, 2020, 2019 and 2018, respectively, for consulting services with certain related parties, including a family member of management and a board member. At both December 31, 2020 and 2019, there was less than $0.1 million included in accounts payable and accrued expenses due to related parties.

8. Stockholders' Equity

Underwritten Offerings

On March 6, 2020, we completed a follow-on offering under our shelf registration statement on Form S-3 pursuant to which we issued an aggregate of 7,187,500 shares of common stock, which included the full exercise of the underwriters' option to purchase additional shares, at a public offering price of $24.00 per share. We received aggregate net proceeds of approximately $161.8 million from the offering after deducting the underwriting discounts and commissions and other offering expenses.

On May 7, 2018, we completed a follow-on offering under our shelf registration statement on Form S-3 (File No. 333-222726) pursuant to which we issued an aggregate of 10,525,424 shares of common stock, which included the full exercise of the underwriters' option to purchase additional shares, at a public offering price of $14.75 per share. We received aggregate net proceeds of approximately $145.7 million from the offering after deducting the underwriting discounts and commissions and other offering expenses.

Open Market Sale Agreement

On August 17, 2018, we entered into an Open Market Sale Agreement (the "Open Market Sale Agreement") with Jefferies LLC, as agent ("Jefferies"), pursuant to which we may issue and sell shares of our common stock having an aggregate offering price of up to $75.0 million from time to time through Jefferies (the "Open Market Offering"). On May 5, 2020, we entered into Amendment No. 1 to the Open Market Sale Agreement, pursuant to which we increased the maximum aggregate offering price of shares of our common stock that we may issue and sell from time to time through Jefferies, by $100.0 million, from $75.0 million to up to $175.0 million (the "Open Market Shares").

Under the Open Market Sale Agreement, Jefferies may sell the Open Market 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 Open Market Shares in amounts and at times to be determined by us from time to time subject to the terms and conditions of the Open Market Sale Agreement, but we have no obligation to sell any of the Open Market Shares in an Open Market Offering.

We or Jefferies may suspend or terminate the offering of Open Market 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 Open Market Shares in the amount of up to 3.0% of gross proceeds from the sale of the Open Market Shares pursuant to the Open Market Sale Agreement. We have also agreed to provide Jefferies with customary indemnification and contribution rights.

During the year ended December 31, 2020, we did not sell any shares under the Open Market Sale Agreement. During the year ended December 31, 2019, we sold an aggregate of 3,712,359 shares of our common stock under the Open Market Sale Agreement, for net proceeds of approximately $46.2 million.

9. Commitments and Contingencies

Operating Leases

We are party to an operating lease of 98,502 square feet of office and research space in Newton, Massachusetts with a term through September 30, 2025 (the "Newton, MA Lease"). 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 $0.6 million. The amount is classified within long-term restricted cash.

Upon the adoption of ASU 2016-02, we recorded an operating lease right-of-use asset of $11.7 million and corresponding lease liability of $16.0 million related only to the Newton, MA Lease. As of December 31, 2018, there was a balance of $1.7 million and $2.6 million related to unamortized deferred rent and tenant incentive allowances, respectively, for the Newton, MA Lease, both accounted for as liabilities. These balances were deducted from the lease liability on the Newton, MA Lease in arriving at the right-of-use asset upon adoption of ASU 2016-02 on January 1, 2019.

The Newton, MA Lease provides for increases in future minimum annual rental payments, as defined in the lease agreement. The Newton, MA Lease also includes real estate taxes and common area maintenance ("CAM") charges in the annual rental payments. As these charges were included in minimum annual rental payments as part of our accounting for the Newton, MA Lease under ASC 840 through December 31, 2018, we have included such amounts in the calculation of the operating lease liability, consistent with ASC 842 and our accounting policy elections thereunder. The operating lease cost for the Newton, MA Lease for both the years ended December 31, 2020 and 2019 was $2.8 million, of which approximately $1.0 million and $0.9 million, respectively, were charges for CAM.

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 insignificant for the years ended December 31, 2020 and 2019.

Lease Commitments

As of December 31, 2020, 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
2021	$ 3,277
2022	3,447
2023	3,718
2024	3,817
2025 and thereafter	2,918
Total minimum lease payments	$ 17,177
Less: present value adjustment	(3,975)
Present value of minimum lease payments	$ 13,202

As of December 31, 2020, the remaining lease term on the Newton, MA Lease was 4.8 years. The lease has a renewal option for an additional five years, although there is no economic penalty for failure to exercise the option. However, because we did not elect the use of hindsight in estimating the lease term for leases subject to transition to the new standard, and the renewal option was not previously considered in our assessment of the lease term for the Newton, MA Lease before adoption of ASC 842, the renewal option was not considered as part of the lease term in calculating the operating lease right-of-use assets and liabilities as of January 1, 2019.

As a discount rate was not directly observable for our Newton, MA Lease, the discount rate used to calculate the net present value of future payments was our incremental borrowing rate calculated at transition based on the remaining lease term. Upon adoption and through December 31, 2020, the discount rate used to calculate the operating lease liability was 11%. The incremental borrowing rate is the rate of interest that we would expect to pay 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 considered (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.

Litigation

From time to time we may face legal claims or actions in the normal course of business. We were named as a defendant in a securities class action litigation filed on July 23, 2019 in the U.S. District Court for the District of Massachusetts. The complaint was filed by the Allegheny County Employees' Retirement System, against us and certain of our current and former executive officers and directors as well as the underwriters of our public offerings of common stock conducted in April 2017 and May 2018. This complaint was voluntarily dismissed on March 12, 2020. A second complaint was filed by Heather Mehdi on September 17, 2019, in the same court and against the same defendants with the exception of the underwriters. In April 2020, the court appointed a lead plaintiff, Myo Thant ("Plaintiff"), who filed an amended complaint on June 29, 2020. The amended complaint alleges violations of federal securities laws based on our disclosures related to the results from the Phase 2 SOPRA study and Part 2 of the Phase 2b STORM study, and seeks unspecified compensatory damages, including interest; reasonable costs and expenses, including attorneys' and expert fees; and such equitable/injunctive relief or other relief as the court may deem just and proper. We have reviewed the allegations and believe they are without merit. We moved to dismiss the complaint on July 31, 2020 and concluded related briefing in September 2020. Before the court ruled on this motion to dismiss, Plaintiff filed a second amended complaint. We moved to dismiss the second amended complaint on November 2, 2020. On December 14, 2020, we were named as a

defendant in a shareholder derivative suit based on allegations substantially similar to those in the class action litigation. The suit was filed in the U.S. District Court for the District of Massachusetts, by Plaintiff Vladimir Gusinsky Revocable Trust, against us and certain of our current and former executive officers and directors. On January 12, 2021, the shareholder derivative suit was stayed pending the outcome of further proceedings in the securities class action. We intend to defend vigorously against this litigation.

10. Product Revenue

To date, our only source of product revenue has been from the U.S. sales of XPOVIO, which we began shipping to our customers in July 2019. 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 at July 3, 2019	$ —	$ —	$ —	$ —
Provision related to sales in the current year	2,657	2,318	234	5,209
Credit and payments made	(1,655)	(499)	—	(2,154)
Ending balance at December 31, 2019	1,002	1,819	234	3,055
Provision related to sales in the current year	9,754	4,263	435	14,452
Credits and payments made	(8,677)	(3,889)	—	(12,566)
Ending balance at December 31, 2020	$ 2,079	$ 2,193	$ 669	$ 4,941

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.

As of December 31, 2020 and 2019, net product revenue of $12.9 million and $7.9 million, respectively, were included in accounts receivable. To date, we have had no bad debt write-offs and we do not currently have credit issues with any customers. There were no credit losses associated with our accounts receivables as of December 31, 2020 and 2019.

11. License and Asset Purchase Agreements

During 2020, we were a party to the following license and other strategic agreements:

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 Antengene's election and the parties' full execution of a manufacturing technology transfer plan and satisfaction of other specified conditions (the "Antengene Manufacturing Election"), we will grant to Antengene non-exclusive rights to manufacture the Antengene Licensed Compounds and products containing such compounds in or outside of the Antengene Territory solely for development and commercialization in the fields in the Antengene Territory.

As part of the Amended Antengene Agreement, Antengene will also have the right to participate in global clinical studies of the Antengene Licensed Compounds and will bear the cost and expense for patients enrolled in 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 specifically necessary to obtain such approvals. Antengene is also responsible for the commercialization of the Antengene Licensed Compounds in the Oncology Field and Non-Oncology Field, as applicable, in the Antengene Territory at its own cost and expense. Until such time as Antengene elects to manufacture its own drug substance, we will furnish clinical supplies of drug substance to Antengene for use in Antengene's development efforts pursuant to a clinical supply agreement between us and Antengene, and Antengene may elect to have us provide commercial supplies of drug product to Antengene pursuant to a commercial supply agreement between us and Antengene, in each case 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 assessed the Amended Antengene Agreement in accordance with ASC 606 and concluded that the amendment was a contract modification. We further concluded that the performance obligations under the Amended Antengene Agreement were the same performance obligations identified in the Original Antengene Agreement, including the following material promises under the contract: (i) exclusive licenses for each Antengene Licensed Compound; (ii) initial data transfers for each Antengene Licensed Compound, which consisted of regulatory data compiled by us for the Antengene Licensed Compounds as of May 2018 (the "Antengene Effective Date"); and (iii) obligations to stand-ready to provide an initial clinical supply for each Antengene Licensed Compound.

We also identified immaterial promises under the contract relating to information exchanges and participation on operating committees and other working groups. Separately, we also identified certain customer options that would create an obligation for us if exercised by Antengene, including (i) additional data transfers for each Antengene Licensed Compound, which would consist of the transfer of additional regulatory data compiled by us for each Antengene Licensed Compound after the Antengene Effective Date; (ii) obligations to provide additional clinical supply and related substance supply for each Antengene Licensed Compound upon request by Antengene; (iii) manufacturing technology transfers and licenses for each Antengene Licensed Compound under the Antengene Manufacturing Election, as detailed above; and (iv) options 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 (the "Antengene Transfer Options"). The

Antengene Transfer Options individually represent material rights, as they were offered at a significant and incremental discount. Therefore, they were further assessed as performance obligations under the Amended Antengene Agreement. Finally, we also identified certain other customer options that would create a manufacturing obligation for us if exercised by Antengene, including for commercial supply. These options do not represent a material right, as they are not offered at a significant and incremental discount.

In further evaluating the promises detailed above, we determined that the exclusive licenses, initial data transfers, and stand-ready obligation to provide initial clinical supply for each Antengene Licensed Compound were not distinct from one another, and must be combined as four separate performance obligations (the "Antengene Combined License Obligation for selinexor," "Antengene Combined License Obligation for eltanexor," "Antengene Combined License Obligation for KPT-9274" and "Antengene Combined License Obligation for verdinexor"). This is because, for each Antengene Licensed Compound, Antengene requires the initial data transfer and initial clinical supply to derive benefit from the exclusive licenses, since we did not grant manufacturing licenses to any of the Antengene Licensed Compounds at contract inception. We also determined that each of the Antengene Transfer Options represents a distinct performance obligation. Based on these determinations, we identified eight performance obligations at the inception of the Antengene License Agreement, including (i) the Antengene Combined License Obligation for selinexor; (ii) the Antengene Combined License Obligation for eltanexor; (iii) the Antengene Combined License Obligation for KPT-9274; (iv) the Antengene Combined License Obligation for verdinexor; and the four components of the Antengene Transfer Options, including (v) the material right for additional data transfer; (vi) the material right for additional clinical supply and related substance supply; (vii) the material right for manufacturing technology transfer and license; and (viii) the material right for the option for a backup compound.

We further determined that the up-front payment of $11.7 million, received upon execution of the Original Antengene Agreement, constituted the entirety of the consideration included in the transaction price at contract inception, which was allocated to the performance obligations based on their relative stand-alone selling prices. We determined that substantially all of the total standalone selling price in the arrangement was derived from the four Antengene Combined License Obligations for selinexor, eltanexor, KPT-9274 and verdinexor. In connection therewith, we also estimated the standalone selling price for each of the material rights within the Antengene Transfer Options, and determined that such amounts were insignificant, and, therefore, immaterial for purposes of allocation. Accordingly, we allocated the $11.7 million transaction price among the Antengene Combined License Obligations as follows: $9.4 million for selinexor, $1.1 million for eltanexor, $1.0 million for KPT-9274, and $0.2 million for verdinexor. We believe that a change in the assumptions used to determine our best estimate of the stand-alone selling prices for any of the identified performance obligations would not have a significant effect on the allocation of the underlying transaction price to the performance obligations.

Under the Original Antengene Agreement, we had already fulfilled all of our promises under the combined performance obligations for selinexor and KPT-9274 as of the effective date of the Amended Antengene Agreement. We recognized $1.0 million under the Original Antengene Agreement during the first quarter of 2020 and had recognized $9.4 million under the Original Antengene Agreement in 2019. Accordingly, the licenses to the incremental territories for selinexor and KPT-9274 were considered distinct from the promised goods and services already provided. By contrast, we have not yet fulfilled all of our promises under the combined performance obligations for eltanexor and verdinexor under the Original Antengene Agreement. Accordingly, the licenses to the incremental territories for eltanexor and verdinexor are not distinct from promised goods and services already provided.

Based on the conclusions noted above, we updated the transaction price, which included the $1.3 million unrecognized deferred revenue from the $11.7 million upfront payment we received from Antengene under the terms of the Original Antengene Agreement, and the $11.7 million upfront payment we received from Antengene under the terms of the Amended Antengene Agreement, and allocated the total, or $13.0 million, to the remaining performance obligations based on their estimated standalone selling prices as of the effective date of the Amended Antengene Agreement. Since we had already fulfilled all of our promises under the combined

performance obligations for selinexor and KPT-9274 as of the effective date of the Amended Antengene Agreement, we recognized a cumulative adjustment to license revenue of $12.7 million during the year ended December 31, 2020. For the remaining promises to be fulfilled under the combined performance obligation for eltanexor, we adjusted short-term deferred revenue to $0.3 million as of December 31, 2020. We will recognize such revenue when initial clinical supply of eltanexor is delivered to Antengene, which we expect to be within twelve months from December 31, 2020. For the remaining promises to be fulfilled under the combined performance obligation for verdinexor, none of the transaction price was allocated thereto, as it was assessed as immaterial in comparison to the other combined performance obligations under the Amended Antengene Agreement.

Finally, we also reassessed other promised goods and services within the modified contract, including customer options and material rights, ultimately concluding such promised goods and services continue to be immaterial. The future development and regulatory milestones and cost reimbursement for providing additional clinical supply of the Antengene Licensed Compounds, all of which represent variable consideration, were evaluated under the most likely amount method, and were not included in the transaction price at contract inception and/or through December 31, 2020, because the amounts were fully constrained as of December 31, 2020. As part of our evaluation of the constraint, we considered numerous factors, including that receipt of such amounts is outside of our control. Separately, any consideration related to sales-based milestones, as well as royalties on net sales upon commercialization of XPOVIO by Antengene, will be recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property licenses granted to Antengene and, therefore, have also been excluded from the transaction price in accordance with the sales-based royalty exception, as well as our accounting policy. We will re-evaluate the transaction price in each reporting period, as uncertain events are resolved, or as other changes in circumstances occur.

During 2020 and 2019, we recognized $13.7 million and $9.4 million, respectively, in revenue under the Amended Antengene Agreement. In addition, in December 2020, we received $9.8 million in regulatory milestone payments from Antengene following certain regulatory filings by Antengene for selinexor in both multiple myeloma and DLBCL indications in Australia, Singapore and South Korea.

Biogen Asset Purchase Agreement

On January 24, 2018, we entered into an Asset Purchase Agreement (the "APA") and Letter Agreement with Biogen MA Inc., a Massachusetts corporation and subsidiary of Biogen, Inc. ("Biogen").

Under the terms of the APA and Letter Agreement, we sold to Biogen exclusive worldwide rights to develop and commercialize our oral SINE compound KPT-350 and certain related assets with an initial focus in amyotrophic lateral sclerosis ("ALS") (the "Transfer of IP"), and also granted Biogen: (i) an exclusive worldwide license under certain of our intellectual property to manufacture or have manufactured KPT-350 (the "Manufacturing License"), (ii) a technology transfer package, consisting of information and our know-how regarding the manufacture of KPT-350 (the "Manufacturing Technology Transfer"), (iii) a right, at Biogen's request, to have us provide transition assistance regarding manufacturing and other matters (the "Transition Assistance"), (iv) existing inventory of KPT-350 (the "Inventory"), (v) an initial supply of KPT-350 (the "Initial Supply"), and (vi) a right, at Biogen's request, to have us manufacture and supply the active pharmaceutical ingredient for an additional supply of KPT-350 (the "Additional Supply"). In consideration for these rights, we received an upfront payment of $10.0 million in 2018, and we are eligible to receive additional payments of up to $142.0 million based on the achievement by Biogen of future specified development and regulatory milestones, and up to $65.0 million based on the achievement by Biogen of future specified commercial milestones. We will also be eligible to receive tiered royalty payments that reach low double-digits based on future net sales until the later of the tenth anniversary of the first commercial sale of the applicable product and the expiration of specified patent protection for the applicable product, determined on a country-by-country basis.

We and Biogen have made customary representations and warranties and agreed to customary covenants in the APA, including covenants requiring Biogen to use commercially reasonable efforts to develop KPT-350 in

specified neurological indications, including ALS, in any of the U.S., United Kingdom, France, Spain, Germany or Italy. The APA will continue in effect until the expiration of all royalty obligations, provided that the APA may be terminated earlier by Biogen, subject to the requirements that Biogen (i) negotiate in good faith with us regarding an assignment or license back to us of the purchased assets and (ii) not transfer or license the purchased assets to a third party unless such third party assumes Biogen's obligations to us under the APA.

We assessed this arrangement in accordance with ASC 606 and concluded that the contract counterparty, Biogen, is a customer. We identified the following material promises in the arrangement: the Transfer of IP and the Manufacturing License. We also identified immaterial promises under the contract that were not deemed performance obligations. We further determined that other promises for Additional Supply and Transition Assistance represented customer options, which would create an obligation for us if exercised by Biogen. Since no additional or material consideration is owed to us by Biogen upon exercise of the customer options for Additional Supply and Transition Assistance, we determined that both are offered at significant and incremental discounts. Accordingly, they were assessed as material rights and, therefore, separate performance obligations in the arrangement. We then determined that the Transfer of IP and the Manufacturing License were not distinct from one another and must be combined as a performance obligation (the "Combined Performance Obligation"). This is because Biogen requires the Manufacturing License to derive benefit from the Transfer of IP. Based on these determinations, as well as the considerations noted above with respect to the material rights for Additional Supply and Transition Assistance, we identified three distinct performance obligations at the inception of the contract: (i) the Combined Performance Obligation, (ii) the material right for Additional Supply, and (iii) the material right for Transition Assistance. We further determined that the up-front payment of $10.0 million constituted the entirety of the consideration included in the transaction price at contract inception, which was allocated to the performance obligations based on their relative stand-alone selling prices. In connection therewith, we estimated the stand-alone selling price of the (i) Combined Performance Obligation, (ii) material right for Additional Supply, and (iii) material right for Transition Assistance, and determined that the stand-alone selling price of the material rights for Additional Supply and Transition Assistance were insignificant based on various quantitative and qualitative considerations. Accordingly, we further determined that the allocation of the transaction price to the material rights for Additional Supply and Transition Assistance was insignificant. Based on the estimates of the stand-alone selling prices for each of the performance obligations, we determined that substantially all of the $10.0 million transaction price should be allocated to the Combined Performance Obligation. We believe that a change in the assumptions used to determine our best estimate of the stand-alone selling prices for the identified performance obligations would not have a significant effect on the allocation of the underlying transaction price to the performance obligations.

Upon execution of the APA, the transaction price included only the $10.0 million up-front payment owed to us. We may receive further payments upon the achievement of certain regulatory and sales milestones, as detailed above, as well as tiered royalty payments that reach low double-digits based on future net sales. We expect to receive the next milestone payment under this agreement, which is $2.0 million, when the fifth patient in a Phase 1 Multiple Ascending Dose Trial in the U.S. of a product in ALS is dosed.

The future development and regulatory milestones, which represent variable consideration, were evaluated under the most likely amount method, and were not included in the transaction price, because the amounts were fully constrained as of December 31, 2020. As part of our evaluation of the constraint, we considered numerous factors, including that receipt of such milestones is outside our control. Separately, any consideration related to sales-based milestones, as well as royalties on net sales upon commercialization by Biogen, will be recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property and, therefore, have also been excluded from the transaction price in accordance with the sales-based royalty exception, as well as our accounting policy. We will re-evaluate the transaction price in each reporting period, as uncertain events are resolved, or as other changes in circumstances occur.

We recognized $10.0 million of revenue during the first quarter of 2018, which was when we had satisfied our promises under the Combined Performance Obligation by transferring the underlying promised goods.

Ono License Agreement

In April 2020, we terminated our October 2017 license agreement with Ono Pharmaceutical Co., Ltd., a corporation organized and existing under the laws of Japan ("Ono"), for the development and commercialization of selinexor and eltanexor for all human oncology indications in Japan, South Korea, Taiwan, Hong Kong, and the countries in the Association of Southeast Asian Nations. Subsequent to termination, all rights to selinexor and eltanexor were returned to us and no further consideration was exchanged between the parties. Accordingly, we recognized $2.2 million in license and other revenue during the year ended December 31, 2020, which represented the deferred revenue on the contract as of the date of termination.

FORUS Therapeutics Inc. Distribution Agreement

In December 2020, we entered into an exclusive distribution agreement ("FORUS Agreement") for the commercialization of XPOVIO in Canada with FORUS Therapeutics Inc. ("FORUS"). Under the terms of the FORUS Agreement, we granted exclusive rights to FORUS as our sole and exclusive distributor of selinexor within Canada (the "FORUS Territory"). Pursuant to the terms of the FORUS Agreement, we received an upfront payment of $5.0 million in the fourth quarter of 2020. We are also eligible to receive additional payments if certain prespecified regulatory and commercial milestones are achieved by FORUS, as well as double-digit royalties on future net sales of XPOVIO in Canada. We have retained the exclusive production rights and will supply finished products to FORUS for commercial use in Canada.

We assessed the FORUS Agreement in accordance with ASC 606 and concluded that the contract counterparty, FORUS, is a customer. We identified the following material promises under the contract: (i) transfer of exclusive rights to distribute XPOVIO in Canada; and (ii) initial data transfer, which consisted of development and regulatory data compiled by us.

We also identified immaterial promises under the contract relating to ongoing regulatory cooperation from us in order to support FORUS in the regulatory approval process. Separately, we also identified a customer option, which is our obligation to provide commercial supply to FORUS throughout the term of the FORUS Agreement. This option does not represent a material right, as it is not offered at a significant and incremental discount.

In further evaluating the promises detailed above, we determined that the exclusive license and initial data transfer were not distinct from one another, and must be combined as a single, distinct performance obligation. We further determined that the up-front payment of $5.0 million, received upon execution of the FORUS Agreement, constituted the entirety of the consideration included in the transaction price at contract inception, which we allocated to the performance obligation. During 2020, we recognized $5.0 million in revenue under the FORUS Agreement, as the performance obligation was satisfied when the initial data transfer was delivered during the fourth quarter.

The future regulatory milestones, which represent variable consideration, were evaluated under the most likely amount method, and were not included in the transaction price at contract inception and/or through December 31, 2020, because the amounts were fully constrained as of December 31, 2020. As part of our evaluation of the constraint, we considered numerous factors, including that the receipt of such amounts is outside of our control. Separately, any consideration related to commercial milestones, as well as royalties on net sales upon commercialization of XPOVIO by FORUS, will be recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property licenses granted to FORUS and, therefore, have also been excluded from the transaction price in accordance with the sales-based royalty exception, as well as our accounting policy. We will re-evaluate the transaction price in each reporting period, as uncertain events are resolved, or as other changes in circumstances occur.

The following revenue was recognized in 2020 that was included as a contract liability as of December 31, 2019 (in thousands):

	December 31, 2019	Additions	Revenue recognized in 2020	December 31, 2020
Short-term Deferred Revenue				
Original Antengene Agreement	$ 2,341	$ —	$ (2,341)	$ —
Amended Antengene Agreement	—	297	—	297
Total short-term deferred revenue	$ 2,341	$ 297	$ (2,341)	$ 297
Long-term Deferred Revenue				
Ono License Agreement	$ 2,192	$ —	$ (2,192)	$ —
Total long-term deferred revenue	$ 2,192	$ —	$ (2,192)	$ —
Total deferred revenue	$ 4,533	$ 297	$ (4,533)	$ 297

12. Stock-based Compensation

In October 2013, the Board adopted and our stockholders approved the 2013 Stock Incentive Plan (the "2013 Plan"), which succeeded our 2010 Stock Incentive Plan, which has expired and under which no further grants will be made. The 2013 Plan provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards and other stock-based awards. The number of shares of common stock reserved for issuance under the 2013 Plan is equal to the sum of (1) 969,696 shares plus (2) the number of shares (up to 2,126,377 shares) equal to the sum of the number of shares of common stock then available for issuance under the 2010 Plan and the number of shares of common stock subject to outstanding awards under the 2010 Plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by us at their original issuance price pursuant to a contractual repurchase right plus (3) an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2014 and continuing until, and including, the fiscal year ending December 31, 2023, equal to the lesser of (A) 1,939,393 shares of common stock, (B) 4% of the number of shares of common stock outstanding on the first day of such fiscal year, or (C) an amount determined by the Board.

In each of the first quarters of 2020, 2019 and 2018, the number of shares available for issuance under the 2013 Plan was increased by 1,939,393 shares of common stock. As of December 31, 2020, we had 1,716,897 shares available for issuance under the 2013 Plan.

During 2020, 2019 and 2018, we also granted stock options through inducement grants outside of our equity compensation plans to certain employees to induce them to accept employment with us (collectively, "Inducement Grants"). The stock options were granted at an exercise price equal to the fair market value of a share of our common stock on the respective grant dates and are exercisable over four years with 25% of the total number of shares underlying the option vesting on the one year anniversary of the respective grant dates and in equal monthly installments thereafter. The foregoing grants were made pursuant to inducement grants outside of our stockholder approved equity plans as permitted under the NASDAQ Stock Market listing rules. We assessed the terms of these awards and determined there was no possibility that we would have to settle these awards in cash and therefore, equity accounting was applied.

Stock-based Compensation Expense

In connection with all share-based payment awards, total stock-based compensation expense recognized was as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Cost of goods sold	$ 126	$ 51	$ —
Research and development	10,215	6,406	8,686
Selling, general and administrative	14,066	8,834	8,589
Total	$ 24,407	$ 15,291	$ 17,275

The total stock-based compensation expense related to employee and non-employee stock options for the years ended December 31, 2020, 2019 and 2018 was $17.0 million, $12.6 million and $16.4 million, respectively. The total stock-based compensation expense related to restricted stock units ("RSU") for the years ended December 31, 2020, 2019 and 2018 was $6.0 million, $1.6 million and $0.4 million, respectively. For the years ended December 31, 2020, 2019 and 2018, we recorded stock-based compensation expense related to the Employee Stock Purchase Plan ("ESPP") of $1.4 million, $1.1 million and $0.4 million, respectively.

Stock Options

The following table summarizes stock option activity related to both the 2013 Plan and Inducement Grants for employees and non-employees:

	Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (year)	Aggregate Intrinsic Value (in thousands)
Options outstanding at December 31, 2019	9,843,094	$ 12.40	7.0	$ 82,134
Granted	3,022,700	17.78		
Exercised	(911,464)	8.13		
Forfeited	(678,014)	14.25		
Options outstanding at December 31, 2020	11,276,316	$ 14.08	6.8	$ 44,028
Options exercisable at December 31, 2020	6,463,238	$ 13.80	5.4	$ 32,154

The total intrinsic value of stock options exercised for the years ended December 31, 2020, 2019 and 2018 was $9.4 million, $2.2 million and $6.0 million, respectively.

The fair value of each stock option granted to employees is estimated on the date of grant and for non-employees on each reporting date and upon vesting using the Black-Scholes option-pricing model. The following table summarizes the assumptions used in calculating the fair value of the awards:

	Year Ended December 31,		
	2020	2019	2018
Volatility	78%-82%	79%-81%	79%-81%
Expected term (in years)	6.0	5.5-6.0	5.5-9.8
Risk-free interest rate	0.30%-1.52%	1.42%-2.58%	2.50%-3.05%
Dividend	—%	—%	—%

We use the simplified method to calculate the expected term as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term for options granted to employees and non-employees. 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 for the year ended December 31, 2020 is based on the historical volatility of our publicly traded stock, given we now have five years of publicly available stock trading activity. Our stock price volatility assumption for the years ended December 31, 2019 and 2018 is based on historical volatility of a representative group of companies with similar characteristics to us and who have similar risk profiles and positions within the industry. 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, 2020, 2019 and 2018 was $12.17, $6.01 and $8.91 per share, respectively.

At December 31, 2020, the total unrecognized compensation related to unvested employee and non-employee stock option awards granted under the 2013 Plan and Inducement Grants was $41.1 million, which we expect to recognize over a weighted-average period of approximately 2.6 years.

Restricted Stock Units

A RSU represents the right to receive one share of our common stock upon vesting of the RSU. The fair value of each RSU is based on the closing price of our common stock on the date of grant. We grant RSUs with service conditions that vest in two or fourequal annual installments provided that the employee remains employed with us.

During the year ended December 31, 2020, we granted 1,375,840 RSUs under the 2013 Plan. The following is a summary of RSU activity for the 2013 Plan for the years ended December 31, 2020 and 2019:

	Number of Shares Underlying RSUs	Weighted-Average Grant Date Fair Value
Unvested at December 31, 2019	787,320	$ 9.28
Granted	1,375,840	17.58
Forfeited	(285,149)	15.57
Vested	(204,288)	9.28
Unvested at December 31, 2020	1,673,723	$ 15.03

As of December 31, 2020, there was $19.5 million of unrecognized compensation costs related to unvested RSUs under the 2013 Plan, which are expected to be recognized over a weighted average period of 2.7 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 six-month offering period, whichever is lower. Purchase dates under the ESPP occur on or about May 1 and November 1 each year.In 2013, our shareholders approved an increase in the number of shares of common stock authorized for issuance pursuant to the ESPP to 242,424 shares of common stock, plus an annual increase 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.

During the years ended December 31, 2020, 2019 and 2018, $2.9 million, $1.7 million and $0.9 million, respectively, was withheld from employees, on an after-tax basis, in order to purchase 249,228, 415,257 and 98,770 shares of our common stock, respectively. As of December 31, 2020, 855,104 shares of our common stock remained available for issuance under the ESPP. As of December 31, 2020, there was $0.5 million of total unrecognized stock-based compensation expense related to the 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 ESPP was estimated using the Black-Scholes option-pricing model with the following weighted-average assumptions:

	Year Ended December 31,		
	2020	2019	2018
Volatility	58%-110%	61%-104%	48%-61%
Expected term (in years)	0.5	0.5	0.5
Risk-free interest rate	0.1%	2.4%-2.5%	1.3%-2.1%
Dividend	—%	—%	—%

13. 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 salary. We contributed a match of $2.9 million, $1.7 million and $1.1 million to the 401(k) Plan for the years ended December 31, 2020, 2019 and 2018, respectively.

14. Income Taxes

For the years ended December 31, 2020, 2019 and 2018, we recorded an income tax expense of $0.3 million, which pertains to income generated by our KPSC entity, as well as foreign income taxes due by our German and Israel subsidiaries, both of which operate on a cost-plus profit margin. The components of our current income tax provision were $0.1 million in state tax expense and $0.2 million in foreign tax expense for the year ended December 31, 2020. Our current income tax provision consisted of less than $0.1 million in foreign income tax expense for the years ended December 31, 2019 and 2018, respectively. We did not have a deferred income tax provision for the years ended December 31, 2020, 2019 and 2018.

The components of loss before income taxes were as follows (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Foreign	$ (37,088)	$ (23,350)	$ (28,689)
U.S.	(158,876)	(176,200)	(149,692)
Totals	$(195,964)	$(199,550)	$(178,381)

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):

	Year Ended December 31,	
	2020	2019
Deferred tax assets:		
U.S. and state net operating loss carryforwards	$ 179,462	$ 150,909
Stock-based compensation	13,814	11,914
Accruals and other temporary differences	4,970	4,212
Research and development credits	75,189	62,374
Capitalized research and development	708	1,021
Fixed assets and intangible assets	9,602	5,893
Deferred revenue	—	1,051
Foreign net operating loss carryforwards	—	4
Lease liability	3,084	3,443
Deferred royalty embedded derivative	421	533
AHYDO Interest	1,017	—
Interest Expense - Sec 163(j)	1,321	—
Unicap - Sec 263A	190	—
Transaction Costs	92	—
Valuation allowance	(275,389)	(224,943)
Total deferred tax assets	14,481	16,411
Deferred tax liabilities:		
Convertible debt amortization	(11,825)	(13,431)
Right-of-use asset	(2,188)	(2,462)
Deferred royalty obligation	(468)	(518)
Total deferred tax liabilities	(14,481)	(16,411)
Net deferred tax assets	$ —	$ —

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, 2020, 2019 and 2018. The valuation allowance increased by approximately $50.5 million during the year ended December 31, 2020 to $275.4 million, from $224.9 million during the year ended December 31, 2019, primarily due to the generation of net operating losses.

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:

	Year Ended December 31,		
	2020	2019	2018
Federal income tax expense at statutory rate	21.0%	21.0%	21.0%
State income tax, net of federal benefit	1.6%	1.7%	0.7%
Permanent differences	(1.0)%	(0.5)%	—%
Research and development credit	6.5%	6.0%	7.8%
Foreign rate differential	(4.1)%	(2.5)%	(3.4)%
Change in valuation allowance	(25.7)%	(25.9)%	(28.2)%
Provision to return adjustments	0.3%	0.6%	2.4%
Other	1.2%	(0.4)%	(0.6)%
Federal rate change	—%	—%	0.3%
Effective Income Tax rate	(0.2)%	—%	—%

As of December 31, 2020, 2019 and 2018, we had U.S. federal net operating loss carryforwards of approximately $698.8 million, $576.5 million and $427.0 million, respectively, which may be able to offset future income tax liabilities. Of the $698.8 million carryforward as of December 31, 2020, $405.9 million of the carryforward has an indefinite life and $292.9 million will expire at various dates through 2037. As of December 31, 2020, 2019 and 2018, we had U.S. state net operating loss carryforwards of approximately $575.2 million, $502.3 million and $414.8 million, respectively, which may be available to offset future state income tax liabilities and expire at various dates through 2040. As of December 31, 2020, 2019 and 2018, we did not have any foreign net operating loss carryforwards to offset future foreign income tax liabilities.

As of December 31, 2020, 2019 and 2018, we had federal research and development tax credit carryforwards of approximately $69.8 million, $58.5 million and $46.9 million, respectively, available to reduce future tax liabilities, which expire at various dates through 2040. As of December 31, 2020, 2019 and 2018, we had state research and development tax credit carryforwards of approximately $6.8 million, $4.9 million and $3.0 million, respectively, available to reduce future tax liabilities, which expire at various dates through 2035. We completed a study of R&D tax credits through December 31, 2019 and adjusted our deferred tax asset for the result of that study. For the year ending December 31, 2020, 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 income tax expense. As of December 31, 2020, 2019 and 2018, 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, 2017 through December 31, 2020. 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.

15. Long-term obligations

3.00% Convertible Senior Notes due 2025

On October 16, 2018, we completed an offering of $150.0 million aggregate principal amount of our 3.00% convertible senior notes due 2025 (the "Notes"). In addition, on October 26, 2018, we issued an additional $22.5 million aggregate principal amount of the Notes pursuant to the full exercise of the option to purchase additional Notes granted to the initial purchasers in the offering. The Notes were sold in a private offering to qualified institutional buyers in reliance on Rule 144A under the Securities Act. In accordance with accounting guidance for debt with conversion and other options, we separately accounted for the liability component ("Liability Component") and the embedded conversion option ("Equity Component") of the Notes by allocating the proceeds between the Liability Component and the Equity Component, due to our ability to settle the Notes in cash, shares of our common stock or a combination of cash and shares of our common stock, at our option. In connection with the issuance of the Notes, we incurred approximately $5.6 million of debt issuance costs, which primarily consisted of underwriting, legal and other professional fees, and allocated these costs between the Liability Component and the Equity Component based on the allocation of the proceeds. Of the total debt issuance costs, $2.2 million was allocated to the Equity Component and recorded as a reduction to additional paid-in capital and $3.4 million was allocated to the Liability Component and recorded as a reduction of the Notes. The portion allocated to the Liability Component is amortized to interest expense using the effective interest method over seven years.

The 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, beginning on April 15, 2019. Upon conversion, the 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 Notes will be subject to redemption at our option, on or after October 15, 2022, in whole or in part, if the conditions described below are satisfied. The 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 Notes may be converted at an initial conversion rate of 63.0731 shares of common stock per $1 principal amount of the Notes (equivalent to an initial conversion price of approximately $15.85 per share of common stock).

Holders of the Notes may convert all or any portion of their Notes, in multiples of $1 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 commencing after the calendar quarter ending on December 31, 2018 (and only during such 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 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 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 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 Notes.

As of December 31, 2020, none of the above circumstances had occurred and as such, the Notes could not have been converted.

We may not redeem the Notes prior to October 15, 2022. On or after October 15, 2022, we may redeem for cash all or part of the 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 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.

The initial carrying amount of the Liability Component of $101.2 million was calculated by measuring the fair value of a similar liability that does not have an associated convertible feature. The allocation was performed in a manner that reflected our non-convertible borrowing rate for similar debt. The Equity Component of the Notes of $67.9 million was recognized as a debt discount and represents the difference between the proceeds from the issuance of the Notes of $172.5 million and the fair value of the liability of the Notes of approximately $104.7 million on their respective dates of issuance. The excess of the principal amount of the Liability Component over its carrying amount is amortized to interest expense using the effective interest method over seven years. The Equity Component is not remeasured as long as it continues to meet the conditions for equity classification.

The outstanding balances of the Notes as of December 31, 2020 consisted of the following (in thousands):

	Outstanding Balances
Liability component:	
Principal	$ 172,500
Less: debt discount and issuance costs, net	(54,572)
Net carrying amount	$ 117,928
Equity component:	$ 65,641

We determined the expected life of the Notes was equal to its seven-year term. The effective interest rate on the Liability Component of the Notes was 11.85%. As of December 31, 2020, the "if-converted value" did not exceed the remaining principal amount of the Notes. The fair value of the Notes was determined based on data points other than quoted prices that are observable, either directly or indirectly, and has been classified as Level 2 within the fair value hierarchy. The fair value of the Notes, which differs from their carrying value, is influenced by market interest rates, our stock price and stock price volatility. The estimated fair value of the Notes as of December 31, 2020 was approximately $215.8 million.

The following table sets forth total interest expense recognized related to the Notes (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Contractual interest expense	$ 5,175	$ 5,175	$ 1,078
Amortization of debt discount	7,685	6,849	1,353
Amortization of debt issuance costs	386	344	68
Total interest expense	$ 13,246	$ 12,368	$ 2,499

Future minimum payments on the Notes as of December 31, 2020 were as follows (in thousands):

Years ended December 31,	Future Minimum Payments
2021	$ 5,175
2022	5,175
2023	5,175
2024	5,175
2025	177,675
Total minimum payments	$ 198,375
Less: interest	(25,875)
Less: unamortized discount	(54,572)
Convertible senior notes	$ 117,928

Deferred Royalty Obligation

In September 2019, we entered into a deferred royalty obligation pursuant to a Revenue Interest Financing Agreement with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. ("HCR") whereby HCR will receive payments from us at a tiered percentage (the "Applicable Tiered Percentage") of future net revenues of XPOVIO and any of our other future products, including worldwide net product sales and upfront payments, milestones, and royalties. We received $75.0 million upon closing (the "First Investment Amount") and have the right to receive an additional $75.0 million (the "Second Investment Amount" and together with the First Investment Amount, the "Investment Amount") upon the achievement of future regulatory and commercial milestones and subject to the approval of both parties and customary closing conditions.

In exchange for the First Investment Amount, HCR will receive tiered royalty payments in the mid-single digits based on worldwide net revenues of XPOVIO and any of our other future products, including worldwide net product sales and upfront payments, milestones, and royalties. The Applicable Tiered Percentages are subject to reduction in the future if a target based on cumulative U.S. net sales is met. Total royalty payments are capped at 185% of the Investment Amount.

If HCR has not received 65% of the Investment Amount by December 31, 2022 or 100% of the Investment Amount by December 31, 2024, we must make a cash payment sufficient to gross up the payments to such minimum amounts.

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 commenced on October 1, 2019 and expires on the earlier of (i) the date in which HCR has received cash payments totaling an aggregate of 185% of the Investment Amount or (ii) the legal maturity date of October 1, 2031. If HCR has not received payments equal to 185% of the Investment Amount by the twelve-year anniversary of the initial closing date, we shall pay an amount equal to the Investment Amount plus a specific annual rate of return less payments previously received by HCR. In the event of a change of control, we are obligated to pay HCR an amount equal to 185% of the Investment Amount less payments previously received by HCR. In addition, upon the occurrence of an event of default, including, among others, our failure to pay any amounts due to HCR under the deferred royalty obligation, 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 Revenue Interest Financing Agreement and our failure to cure the breach within the prescribed time frame, we are obligated to pay HCR an amount equal to 185% of the Investment Amount less payments previously received by HCR. In addition, upon an event of default, HCR may exercise all other rights and remedies available under the Revenue Interest Financing Agreement, including foreclosing on the collateral that was pledged to HCR, which consists of all of our present and future assets relating to XPOVIO.

We have evaluated the terms of the deferred royalty obligation and concluded that the features of the Investment Amount are similar to those of a debt instrument. Accordingly, we have accounted for the transaction as long-term debt. We have further evaluated the terms of the debt and determined that the repayment of 185%of the Investment Amount, less any payments made to date, upon a change of control is an embedded derivative that requires bifurcation from the debt instrument and fair value recognition. We determined the fair value of the derivative using an option pricing Monte Carlo simulation model taking into account the probability of change of control occurring and potential repayment amounts and timing of such payments that would result under various scenarios, as further described in Note 2, "*Summary of Significant Accounting Policies"*. The aggregate fair value of the embedded derivative was $1.8 million and $2.3 million as of December 31, 2020 and 2019, respectively. We recorded a $0.5 million gain on the embedded derivative in other (income) expense, net during 2020 and did not incur a gain or loss on the embedded derivative during 2019. We will remeasure the embedded derivative to fair value each reporting period until the time the features lapse and/or termination of the deferred royalty obligation.

The effective interest rate as of December 31, 2020 was 18.5%. In connection with the deferred royalty obligation, we incurred debt issuance costs totaling $1.4 million. Debt issuance costs 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 assumptions used in determining the expected repayment term of the debt and amortization period of the issuance costs requires that we make estimates that could impact the short and long-term classification of these costs, as well as the period over which these costs will be amortized.

The carrying value of the deferred royalty obligation at December 31, 2020 and 2019 was $71.3 million based on $75.0 million of proceeds, net of the fair value of the bifurcated embedded derivative liability upon execution of the Revenue Interest Financing Agreement, and debt issuance costs incurred. The carrying value of the deferred royalty obligation approximates fair value at December 31, 2020 and 2019 and was measured using Level 3 inputs. The estimated fair market value was calculated using an option pricing Monte Carlo simulation model with inputs consistent with those used in determining the embedded derivative values as described in Note 2 "*Summary of Significant Accounting Policies"*.

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
3.1	Restated Certificate of Incorporation of the Registrant, as amended (incorporated by reference to Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2019)
3.2	Second 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 17, 2020)
4.1	Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 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)
4.2	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)
4.3	Description of Securities Registered under Section 12 of the Exchange Act
10.1*	2010 Stock Incentive Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)
10.2*	Forms of Non-Qualified Stock Option Agreement under 2010 Stock Incentive Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)
10.3*	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)
10.4*	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 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)
10.5*	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)
10.6*	Form of Restricted Stock Unit Agreement under the 2013 Stock Incentive Plan (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 9, 2015)
10.7*	Form of Nonstatutory Stock Option Agreement for Inducement Grants (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 10, 2018)
10.8*	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)
10.9*	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)

Exhibit Number	Description of Exhibit
10.10*	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)
10.11*	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)
10.12*	2020 Israeli Equity Incentive Sub Plan to the 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.13 to the Registrant's Quarterly Report on Form 10-Q (File No.001-36167) filed with the Commission on November 2, 2020)
10.13*	Form of Option Agreement under 2020 Israeli Equity Incentive Sub Plan to the 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.14 to the Registrant's Quarterly Report on Form 10-Q (File No.001-36167) filed with the Commission on November 2, 2020)
10.14*	Form of Restricted Stock Unit Agreement under 2020 Israeli Equity Incentive Sub Plan to the 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.15 to the Registrant's Quarterly Report on Form 10-Q (File No.001-36167) filed with the Commission on November 2, 2020)
10.15*	2013 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.6 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)
10.16*	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)
10.17*	Amended and Restated Letter Agreement, dated as of August 31, 2020, between the Registrant and Michael Kauffman, M.D., Ph.D. (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 31, 2020)
10.18*	Amended and Restated Letter Agreement, dated as of August 31, 2020, between the Registrant and Sharon Shacham, Ph.D., M.B.A. (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 31, 2020)
10.19*	Amended and Restated Letter Agreement, dated as of August 31, 2020, between the Registrant and Christopher B. Primiano (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 31, 2020)
10.20*	Transition Agreement, dated as of September 25, 2020, between the Registrant and Christopher B. Primiano (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 September 25, 2020)
10.21*	Consulting Agreement, dated as of September 25, 2020, between the Registrant and Christopher B. Primiano (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 September 25, 2020)
10.22*	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)

Exhibit Number	Description of Exhibit
10.23*	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)
10.24*	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)
10.25	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)
10.26	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)
10.27	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)
10.28	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)
10.29	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)
10.30	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)
10.31	Open Market Sale Agreement, dated August 17, 2018, by and between the Registrant and Jefferies 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 August 17, 2018)
10.32	Amendment No. 1 to the Open Market Sale Agreement, by and between the Registrant and Jefferies LLC, dated May 5, 2020 (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 5, 2020)
10.33†	Asset Purchase Agreement, dated January 24, 2018, by and between the Registrant and Biogen MA Inc. (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 10, 2018)
10.34†	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)
10.35***	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 8, 2020).

Exhibit Number	Description of Exhibit
10.36	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)
10.37*	Karyopharm Therapeutics Inc. Annual Bonus Plan (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 6, 2019)
10.38***	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)
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 Senior 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 Michael G. Kauffman, M.D., Ph.D., Chief Executive Officer of the Registrant, and Michael Mason, Senior Vice President, Chief Financial Officer and Treasurer of the Registrant
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 Schema Document
101.CAL	Inline XBRL Calculation Linkbase Document
101.LAB	Inline XBRL Labels Linkbase Document
101.PRE	Inline XBRL Presentation Linkbase Document
101.DEF	Inline XBRL Definition Linkbase 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.
** Filed with this Annual Report on Form 10-K.
*** Certain portions of this exhibit (indicated by "***") 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 24, 2021

KARYOPHARM THERAPEUTICS INC.

By: /s/ Michael G. Kauffman
Michael G. Kauffman, M.D., Ph.D.
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/ Michael G. Kauffman Michael G. Kauffman, M.D., Ph.D.	Chief Executive Officer and Director (Principal Executive Officer)	February 24, 2021
/s/ Michael Mason Michael Mason	Senior Vice President, Chief Financial Officer and Treasurer (Principal Financial and Accounting Officer)	February 24, 2021
/s/ Garen G. Bohlin Garen G. Bohlin	Director	February 24, 2021
/s/ Mikael Dolsten Mikael Dolsten, M.D., Ph.D.	Director	February 24, 2021
/s/ Barry E. Greene Barry E. Greene	Director	February 24, 2021
/s/ Mansoor Raza Mirza Mansoor Raza Mirza	Director	February 24, 2021
/s/ Christy J. Oliger Christy J. Oliger	Director	February 24, 2021
/s/ Deepika R. Pakianathan Deepika R. Pakianathan Ph.D.	Director	February 24, 2021
/s/ Richard Paulson Richard Paulson	Director	February 24, 2021
/s/ Chen Schor Chen Schor	Director	February 24, 2021

DESCRIPTION OF SECURITIES REGISTERED UNDER SECTION 12 OF THE EXCHANGE ACT

The following description of the common stock, $0.0001 par value per share (the "Common Stock"), of Karyopharm Therapeutics Inc. ("us," "our," "we" or the "Company"), which is the only security of the Company registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), summarizes certain information regarding the Common Stock in our certificate of incorporation, our by-laws and applicable provisions of the Delaware General Corporation Law (the "DGCL"), and is qualified by reference to our certificate of incorporation and by-laws, which are incorporated by reference as Exhibit 3.1 and Exhibit 3.2, respectively, to the Annual Report on Form 10-K of which this Exhibit 4.3 is a part.

Authorized Capital Stock

Our authorized capital stock consists of 200,000,000 shares of Common Stock and 5,000,000 shares of preferred stock, $0.0001 par value per share (the "Preferred Stock").

Common Stock

Annual Meeting. Annual meetings of our stockholders are held on the date designated in accordance with our by-laws. Written notice must be mailed to each stockholder entitled to vote not less than ten nor more than 60 days before the date of the meeting. The presence in person or by proxy of the holders of record of a majority of our issued and outstanding shares entitled to vote at such meeting constitutes a quorum for the transaction of business at meetings of the stockholders. Special meetings of the stockholders may be called for any purpose by the board of directors, the chairman of the board or the chief executive officer. Except as may be otherwise provided by applicable law, our certificate of incorporation or our by-laws, all elections shall be decided by a plurality, and all other questions shall be decided by a majority, of the votes cast by stockholders entitled to vote thereon at a duly held meeting of stockholders at which a quorum is present.

Voting Rights. Each holder of Common Stock is entitled to one vote for each share held of record on all matters to be voted upon by stockholders.

Dividends. Subject to the rights, powers and preferences of any outstanding Preferred Stock, and except as provided by law or in our certificate of incorporation, dividends may be declared and paid or set aside for payment on the Common Stock out of legally available assets or funds when and as declared by the board of directors.

Liquidation and Dissolution. Subject to the rights, powers and preferences of any outstanding Preferred Stock, in the event of our liquidation or dissolution, our net assets will be distributed pro rata to the holders of our Common Stock.

Other Rights. Holders of the Common Stock have no right to:

- convert the stock into any other security;
- have the stock redeemed;
- purchase additional stock; or
- maintain their proportionate ownership interest.

The Common Stock does not have cumulative voting rights. The rights, preferences and privileges of the holders of Common Stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of Preferred Stock that we may designate and issue. Holders of shares of the Common Stock are not required to make additional capital contributions.

Provisions of Our Certificate of Incorporation and By-laws and the DGCL That May Have Anti-Takeover Effects

Board of Directors. Our certificate of incorporation and by-laws provide for a board of directors divided as nearly equally as possible into three classes. Each class is elected to a term expiring at the annual meeting of stockholders held in the third year following the year of such election. The number of directors comprising our board of directors is fixed from time to time by the board of directors.

Removal of Directors by Stockholders. Our certificate of incorporation and by-laws provide that, subject to the rights of holders of any series of Preferred Stock, a member of our board of directors may only be removed for cause and only by an affirmative vote of the holders of at least 75% of the outstanding shares entitled to vote on the election of the directors.

Super-Majority Voting. The DGCL provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or by-laws, unless a corporation's certificate of incorporation or by-laws, as the case may be, requires a greater percentage. Subject to the rights of holders of any series of Preferred Stock, our by-laws may be amended or repealed by a majority vote of our board of directors or the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal, or to adopt any provisions inconsistent with, any of the provisions of our certificate of incorporation described under the prior two paragraphs.

Stockholder Nomination of Directors. Our by-laws provide that a stockholder must notify us in writing of any stockholder nomination of a director not earlier than 120 days but not later than 90 days prior to the first anniversary of the preceding year's annual meeting; provided, that if the date of the annual meeting is advanced by more than 20 days, or delayed by more than 60 days, from such anniversary date, notice by the stockholder to be timely must be so delivered not earlier than the 120th day prior to the date of such annual meeting and not later than close of business on the later of (x) the 90th day prior to the date of such meeting and (y) the 10th day following the day on which notice of the date of such annual meeting was mailed or public announcement of the date of such annual meeting is first made by us, whichever occurs first.

No Action By Written Consent. Our certificate of incorporation and our by-laws provide that our stockholders may not act by written consent and may only act at duly called meetings of stockholders. Our certificate of incorporation and our by-laws also provide that, except as otherwise required by law, special meetings of our stockholders can only be called by our board of directors, chairman of the board or chief executive officer. In addition, our by-laws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of candidates for election to our board of directors.

Issuance of Preferred Stock. Our board of directors is authorized, without further action by our stockholders, to issue up to 5,000,000 shares of Preferred Stock in one or more series, and to fix the designations, powers, preferences and the relative, participating, optional or other special rights, and any qualifications, limitations and restrictions of the shares of each series of Preferred Stock. The issuance of Preferred Stock could impede the completion of a merger, tender offer or other takeover attempt.

Delaware Business Combination Statute. We are subject to Section 203 of the DGCL. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless the interested stockholder attained such status with the approval of the corporation's board of directors or unless the business combination is approved in a prescribed manner or the interested stockholder acquired at least 85% of the corporation's outstanding voting stock in the transaction in which it became an interested stockholder. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and the sale of more than 10% of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Exclusive Forum Selection. Our by-laws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) shall, to the fullest extent permitted by law, be the sole and exclusive forum for: (i) any derivative action or proceeding brought on behalf of the Company, (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer, other employee or stockholder of the Company to the Company or the Company's stockholders, (iii) any action asserting a claim arising pursuant to any provision of the General Corporation Law of the State of Delaware or as to which the General Corporation Law of the State of Delaware confers jurisdiction on the Court of Chancery of the State of Delaware, or (iv) any action asserting a claim arising pursuant to any provision of our certificate of incorporation or our by-laws or governed by the internal affairs doctrine; provided, however, that this exclusive forum provision shall not apply to claims arising under the Securities Act of 1933 or the Securities Exchange Act of 1934 or any other claim for which the federal courts have exclusive jurisdiction. In addition, unless the Company consents in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any claims arising under the Securities Act of 1933.

Exhibit 21.1

Subsidiaries of Karyopharm Therapeutics Inc.

	Jurisdiction of Incorporation or Organization
Karyopharm Securities Corp.	Massachusetts
Karyopharm Europe GmbH	Germany
Karyopharm Therapeutics (Bermuda) Ltd.	Bermuda
Karyopharm Israel Ltd.	Israel

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

1. Registration Statement (Form S-8, File No. 333-194746) pertaining to the 2010 Stock Incentive Plan of Karyopharm Therapeutics Inc., 2013 Stock Incentive Plan of Karyopharm Therapeutics Inc., and 2013 Employee Stock Purchase Plan of Karyopharm Therapeutics Inc.;
2. Registration Statements (Form S-8, File Nos. 333-202742, 333-216732, and 333-223675) pertaining to the 2013 Stock Incentive Plan of Karyopharm Therapeutics Inc.;
3. Registration Statements (Form S-8, File Nos. 333-210221, 333-229971 and 333-237160) pertaining to the 2013 Stock Incentive Plan of Karyopharm Therapeutics Inc. and 2013 Employee Stock Purchase Plan of Karyopharm Therapeutics Inc.;
4. Registration Statements (Form S-3, File Nos. 333-226038 and 333-236639) and related Prospectuses of Karyopharm Therapeutics Inc. for the registration of debt securities, common stock, preferred stock, warrants, and units;
5. Registration Statement (Form S-8, File No. 333-226639) pertaining to Inducement Stock Option Awards (September 2017 – July 2018) of Karyopharm Therapeutics Inc.;
6. Registration Statement (Form S-8, File No. 333-233094) pertaining to Inducement Stock Option Awards (August 2018 – July 2019) of Karyopharm Therapeutics Inc.; and
7. Registration Statement (Form S-8, File No. 333-248357) pertaining to Inducement Stock Option Awards (August 2019 – July 2020) of Karyopharm Therapeutics Inc.;

of our reports dated February 24, 2021, with respect to the consolidated financial statements of Karyopharm Therapeutics Inc., and the effectiveness of internal control over financial reporting of Karyopharm Therapeutics Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2020.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 24, 2021

Exhibit 31.1

Certification

I, Michael G. Kauffman, M.D., Ph.D., certify that:

1. I have reviewed this Annual Report on Form 10-K of Karyopharm Therapeutics Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 24, 2021

/s/ Michael G. Kauffman

Michael G. Kauffman, M.D., Ph.D.
Chief Executive Officer

Exhibit 31.2

Certification

I, Michael Mason, certify that:

1. I have reviewed this Annual Report on Form 10-K of Karyopharm Therapeutics Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 24, 2021

/s/ Michael Mason

Michael Mason
Senior Vice President, Chief Financial Officer and Treasurer
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with this Annual Report on Form 10-K of Karyopharm Therapeutics Inc. (the "Company") for the year ended December 31, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers of the Company hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: February 24, 2021

/s/ Michael G. Kauffman
Michael G. Kauffman, M.D., Ph.D.
Chief Executive Officer

/s/ Michael Mason
Michael Mason
Senior Vice President, Chief Financial Officer and Treasurer
(Principal Financial and Accounting Officer)