

**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, 2019**
- 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
(State or other jurisdiction of
incorporation or organization)

26-3931704
(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)
Common Stock, \$0.0001 par value

Trading Symbol(s)
KPTI

(Name of each exchange on which listed)
Nasdaq Global Select Market

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

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

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

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

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

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

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

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of 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, 2019 was approximately \$343,517,677. Shares of common stock held by each executive officer and director and by each holder of 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

Number of shares outstanding of the registrant's Common Stock as of February 14, 2020: 65,548,095.

Documents incorporated by reference:

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 29, 2020 in connection with our 2020 annual meeting of stockholders 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, our commercialization efforts, our partnerships 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 those inherent in pharmaceutical research and development, such as our ability to successfully commercialize XPOVIO® (selinexor), adverse results in our drug discovery and clinical development activities, decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates, our ability to raise additional capital to support our clinical development program and other operations, our ability to develop products of commercial value and to identify, discover and obtain rights to additional potential product candidates, our ability to obtain, maintain and enforce intellectual property rights for our drug candidates, dependence on any collaborators, competition, our ability to obtain any necessary financing to conduct our planned activities, and other risk factors. Please refer to the section entitled “Risk Factors” in Part I of this report for a description of these risks and uncertainties. Unless required by law, we do not undertake any obligation to update any forward-looking statements.

PART I

Item 1. Business

BUSINESS

Overview

We are an innovation-driven pharmaceutical company focused on the discovery, development and commercialization of novel, first-in-class drugs directed against nuclear transport and related targets for the treatment of cancer and other major 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 **Selective Inhibitor of Nuclear Export (SINE)** compounds that inhibit the nuclear export protein exportin 1, or XPO1. These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of high unmet medical need diseases. Our SINE compounds were the first oral XPO1 inhibitors in clinical development. Our lead asset, XPOVIO® (selinexor) tablets, was the first SINE compound to receive marketing approval by the U.S. Food and Drug Administration, or FDA, on July 3, 2019 and is currently indicated for use in 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, or PIs, at least two immunomodulatory agents, or IMiDs, and an anti-CD38 monoclonal antibody. We refer to myeloma that is refractory to these five agents as penta-refractory myeloma. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. The ongoing, randomized Phase 3 BOSTON (**B**ortezomib, **S**elinexor and **D**examethasone) study evaluating selinexor in combination with Velcade® (bortezomib) and low-dose dexamethasone in patients with myeloma treatment with between one and three prior therapies is expected to serve as the confirmatory trial.

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Our focus is on marketing XPOVIO in its currently approved indication 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 conduct additional clinical trials and seek additional approvals for the use of selinexor in combination with other oncology therapies to expand the patient populations that are eligible for selinexor. Thus, we are currently advancing the clinical development of selinexor in multiple hematological malignancies and solid tumor indications. Studies that support submitted applications for regulatory approval include STORM (Selinexor Treatment of Refractory Myeloma) and SADAL (Selinexor Against Diffuse Aggressive Lymphoma). Ongoing clinical trials evaluating selinexor include the pivotal, randomized Phase 3 BOSTON study in multiple myeloma, the Phase 1b/2 STOMP (Selinexor and Backbone Treatments of Multiple Myeloma Patients) study in combination with standard therapies in multiple myeloma, the Phase 2/3 SEAL (Selinexor in Advanced Liposarcoma) study in liposarcoma, and the Phase 3 SIENDO (Selinexor/Placebo After Combination Chemotherapy In Patients with Advanced or Recurrent Endometrial Cancer) study evaluating selinexor as maintenance therapy in endometrial cancer. During 2019, final data from the Phase 2b STORM study were published in the *New England Journal of Medicine* (Chari, A. *et al.* August 2019). In addition, we reported updated, positive data from the SADAL study as well as updated interim data for the STOMP study at various medical conferences. As a result of the positive results from STORM, in addition to the FDA approval of our first New Drug Application, or NDA, we also filed a Marketing Authorization Application, or MAA, with the European Medicines Agency, or EMA, in January 2019 and expect to receive a decision on our application in the middle of 2020.

Based on the positive results of the SADAL study, we submitted a Supplemental New Drug Application, or sNDA, to the FDA in December 2019, with a request for accelerated approval for selinexor as a new treatment for adult patients with relapsed and/or refractory diffuse large B-cell lymphoma, or DLBCL, not otherwise specified, who have received at least two prior therapies. The FDA accepted the application for filing on February 18, 2020 and granted Priority Review with a target decision date of June 23, 2020 under the Prescription Drug User Fee Act, or PDUFA. Selinexor has received both Orphan Drug and Fast Track designations from the FDA for this same indication. Provided that marketing approval is granted by the FDA, we expect to be prepared to commercialize selinexor in the United States as a treatment for patients with relapsed and/or refractory DLBCL as early as the middle of 2020. We also plan to submit a MAA to the EMA in 2020 with a request for conditional approval.

In addition to selinexor, we are also advancing a pipeline of novel drug candidates including our other oral SINE compounds eltanexor (KPT-8602) and verdinexor (KPT-335), as well as our oral dual PAK4/NAMPT inhibitor, KPT-9274. We began clinical testing of eltanexor, a second-generation SINE compound, in late 2015. Our clinical development program for eltanexor includes myelodysplastic syndrome, or MDS, colorectal cancer, or CRC, and metastatic castration-resistant prostate cancer, or CRPC. Based on clinical results to date and resource prioritization, we plan to focus on the development of eltanexor in MDS in 2020. We began clinical testing of KPT-9274 in patients with hematologic or solid tumors during 2016 and we plan to study its combination with an anti-PD1 monoclonal antibody in a phase 1 clinical study in the near future. Finally, verdinexor is our lead compound that is being evaluated as a potential therapy for viral, rare disease and autoimmune indications in humans and by a collaborator as a potential therapy for cancers in companion animals.

FDA Accelerated Approval of XPOVIO

Following the positive outcome from the expanded cohort of the STORM study, on August 6, 2018, we announced the completion of the rolling submission of an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for patients with heavily pretreated, relapsed or refractory multiple myeloma. On October 5, 2018, the FDA accepted for filing our NDA and also granted our request for priority review of the NDA and assigned an action date of April 6, 2019 under the PDUFA. On February 26, 2019, the Oncologic Drugs Advisory Committee, or ODAC, of the FDA met to review data supporting our NDA requesting accelerated approval for selinexor. The FDA specifically asked the ODAC to vote on whether the

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committee believed the approval of selinexor should be delayed until the results from the ongoing, randomized Phase 3 BOSTON study are available. In a vote of eight “Yes” and five “No,” the ODAC recommended that the approval decision for selinexor should be delayed until the results of the BOSTON study are available.

Following the ODAC meeting, and at the FDA’s request, we submitted additional, existing clinical information that included preliminary data from the BOSTON study as an amendment to the NDA, which allowed the FDA to extend the PDUFA action date by three months to July 6, 2019. On July 3, 2019, the FDA approved oral XPOVIO, our first-in-class, nuclear export inhibitor. XPOVIO was approved in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 monoclonal antibody. XPOVIO is the first SINE compound and is the first ever nuclear export inhibitor approved for human use. The first indication is approved under accelerated approval based on response rate. As with all accelerated approvals, continued approval for the treatment of myeloma may be contingent upon verification and description of clinical benefit in a confirmatory trial. The ongoing Phase 3 BOSTON study is expected to serve as the confirmatory trial for the accelerated approval of XPOVIO. The FDA noted in its press release announcing the approval of XPOVIO that the efficacy evaluation was supported by additional information from the BOSTON study.

Commercialization of XPOVIO in the U.S.

In July 2019, XPOVIO became commercially available to patients in the U.S. The commercial launch of XPOVIO is being supported by approximately 70 Karyopharm sales representatives and nurse liaisons as well as KaryForward™, an extensive patient and healthcare provider support program. Our commercial efforts are also being supplemented by patient support initiatives coordinated by our dedicated network of participating specialty pharmacy providers.

As of December 31, 2019, approximately 1,400 XPOVIO prescriptions had been fulfilled, driven by strong demand from both academic and community-based oncologists, and XPOVIO had been prescribed by more than 550 unique physicians and healthcare accounts. Net product sales for XPOVIO were \$30.5 million through December 31, 2019. XPOVIO sales have been driven by a combination of new patient starts, prescription refills, and initial channel inventory to our distribution partners. Patient demand for XPOVIO continued to increase during 2019 following its accelerated approval by the FDA. Prompt insurance coverage for XPOVIO has been a key contributor to its early commercial success, with XPOVIO being added to numerous national commercial and Medicare formularies and coverage policies.

In 2020, we expect to build upon XPOVIO’s early commercial success in the late-line relapsed refractory multiple myeloma market by educating physicians, healthcare providers and patients about XPOVIO’s clinical profile and unique mechanism of action. Additionally, if results from the pivotal BOSTON trial, which are expected in early 2020, are positive, our commercial team will begin to prepare for XPOVIO’s potential expansion into the second line relapsed refractory multiple myeloma market, subject to the FDA’s review and approval of our expected sNDA. Finally, pending FDA approval of XPOVIO in DLBCL, we expect to begin selling XPOVIO in this indication to hematologists and oncologists in the U.S with our existing field sales force.

European Marketing Authorization Application

In January 2019, we submitted a MAA to the EMA requesting conditional approval for selinexor in combination with dexamethasone as a new treatment for patients with triple class refractory multiple myeloma, meaning patients who have received at least three prior therapies and whose disease is refractory to at least one PI, one IMiD, and one anti-CD38 monoclonal antibody. This submission was based on the positive results from the Phase 2b STORM study. We received feedback from EMA’s Committee for Medicinal Products for Human Use, or CHMP, including the integrated inspection report, based on site audits and a sponsor inspection. In January 2020, we were granted a three-month extension from CHMP to provide additional time to respond to the

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CHMP’s outstanding questions related to the application. We are currently working with CHMP to address the outstanding questions and expect to receive a decision on the application in mid-2020.

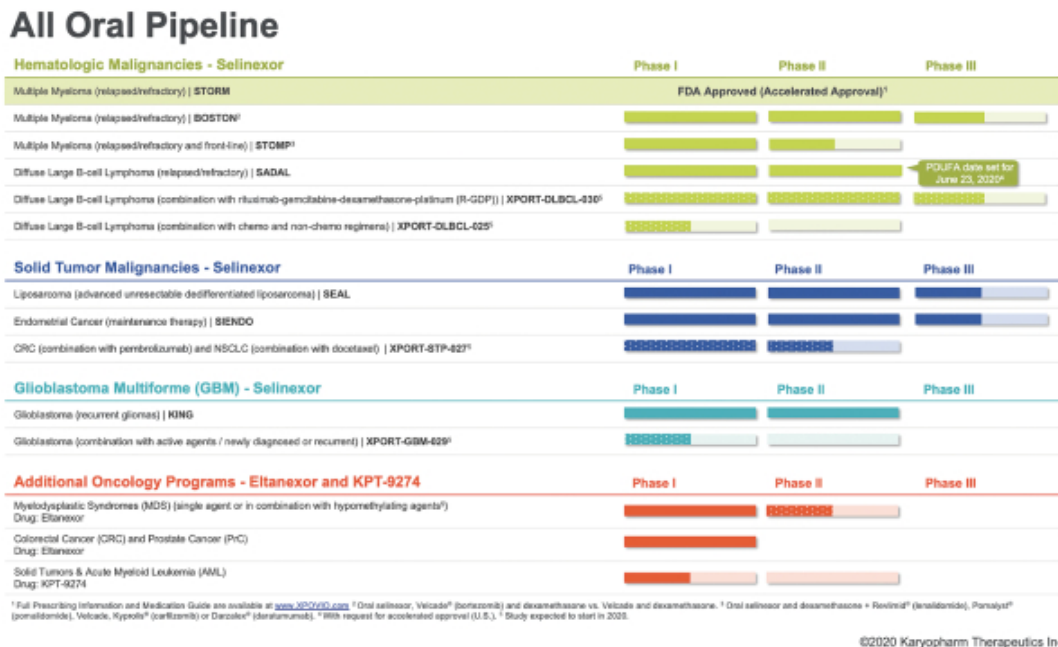
To commercialize selinexor following any regulatory approval outside of the U.S., we will either work with existing and potential future partners to establish the appropriate commercial infrastructure outside the U.S., or we may, in certain geographies, elect to establish the commercial infrastructure ourselves.

Randomized Confirmatory BOSTON Study in Multiple Myeloma

We are currently conducting the pivotal, randomized Phase 3 BOSTON study evaluating once-weekly selinexor in combination with once-weekly Velcade and dexamethasone (SVd) for the treatment of patients with multiple myeloma who have had one to three prior lines of therapy. Enrollment in the BOSTON study was completed in January 2019 and top-line data are expected in early 2020, contingent upon the occurrence of progression-free survival, or PFS, events, the primary endpoint of the study. Data from the BOSTON study, if positive, are expected to be used to support regulatory submissions to the FDA, the EMA and other regulatory agencies requesting the use of selinexor in combination with Velcade and dexamethasone in patients with multiple myeloma who have received at least one prior line of therapy. If approved, this combination of selinexor with Velcade and dexamethasone will be the first approved therapy using once weekly (rather than the standard twice weekly) dosing of Velcade. Given that Velcade must be given in a healthcare setting, we believe that this once-weekly dosing regimen could be substantially more attractive to patients by potentially eliminating a significant percentage of office visits.

Summary of Karyopharm’s Pipeline and Core Clinical Trials

Key clinical trials of selinexor are summarized in the chart below. In addition to these studies, there are several ongoing investigator-sponsored clinical trials in a variety of hematological and solid tumor malignancies.



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.

Hematological Malignancies

Multiple Myeloma

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. It is more common in elderly patients, with a median age at diagnosis of 69 years. According to the National Cancer Institute, or NCI, multiple myeloma is the second most common cancer of the blood in the U.S. with more than 32,000 new cases each year and over 130,000 patients living with the disease. 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 in the last 20 years due to the use of high-dose chemotherapy and autologous stem cell transplantation, which is restricted to healthier, often younger patients, and the subsequent introduction of IMiDs, such as Revlimid and Pomalyst, and the PIs Velcade, Kyprolis[®], and Ninlaro[®] (ixazomib). Two monoclonal antibodies, Darzalex and Emluciti[™] (elotuzumab), 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 in relapsed and/or refractory patients, including new proteasome inhibitors (oprozomib and marizomib), monoclonal antibodies (with or without toxin conjugates; belantamab mafodotin, an anti-BCMA antibody-drug conjugate; isatuximab, an anti-CD38 monoclonal antibody) and cellular therapies like chimeric antigen receptor T-cell, or CAR-T, therapy, nearly all patients will eventually relapse and succumb to their disease. With about 13,000 deaths from multiple myeloma in the United States alone expected to occur in 2020 according to the American Cancer Society, we believe that there remains a need for therapies for patients whose disease has relapsed after, or is refractory to, available therapy. The approval of XPOVIO in patients with penta-refractory myeloma after four prior therapies further supports this perspective.

According to EvaluatePharma (January 2020), the worldwide market for prescription drugs used to treat patients with multiple myeloma exceeded \$16 billion in 2018 and is projected to reach over \$20 billion by 2024.

The Phase 2b STORM Study

The Phase 2b STORM study was a single-arm clinical trial evaluating oral selinexor in combination with standard, low-dose dexamethasone in patients with heavily pretreated, relapsed or refractory myeloma. Based on the results of the clinical data set for Part 1 of the STORM study, which we reported in 2016, we expanded the STORM study, designated Part 2, which enrolled 122 heavily pretreated patients with triple-class refractory myeloma, of which 83 patients had penta-refractory myeloma.

The results from the STORM study served as the basis for our NDA filing and subsequent accelerated approval from the FDA. The final data from the 122 patients treated on STORM Part 2 were published in the *New England Journal of Medicine* on August 22, 2019. 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 documented to be refractory to all five major agents and is designated 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.

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Given the rapid progression of triple-class refractory myeloma, the window of opportunity to prevent further illness and death is small. Therefore, the regimen that was used in the STORM study began with a high dose of selinexor to achieve rapid disease control. Each patient began treatment with 80mg oral selinexor twice weekly in combination with low-dose dexamethasone (20mg twice weekly). This initial dose was chosen to optimize the potential to halt disease progression and reduce tumor load. Because most patients involved in the study had limited end-organ reserve and were at increased risk for adverse events, dose modifications were anticipated and were specified along with supportive care in the study protocol.

For the STORM study's primary endpoint, oral selinexor achieved an ORR of 26%, including two (2%) stringent complete responses, or sCRs, six (5%) very good partial responses, or VGPRs, and 24 (20%) partial responses, or 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, or 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 Independent Review Committee consisting of 4 independent experts in the treatment of multiple myeloma.

Median duration of response, or DOR, was 4.4 months. PFS was 3.7 months and overall survival, or 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 adverse events that were observed in the study appeared to be a function of dose, schedule, and baseline clinical characteristics, including, for example, preexisting cytopenias. The most common treatment-emergent adverse events, or AEs, were thrombocytopenia (73%), fatigue (73%), nausea (72%) and anemia (67%). AEs are classified by severity and graded on a scale of one to five with one being the least severe and five resulting in death. The most common Grade 3/4 treatment-emergent AEs were thrombocytopenia (59%), anemia (44%), hyponatremia (22%) and neutropenia (21%). Importantly, most non-hematologic AEs were limited in severity to Grades 1 or 2, with only 10% experiencing Grade 3 nausea and 3% experiencing Grade 3 vomiting. In all, 18% of patients discontinued study treatment because of an AE considered by the investigator related to the study drug. AEs leading to dose modification or holds occurred in 80% of patients, with the majority occurring in the first two months of treatment. The most common AEs leading to dose reduction or interruption were thrombocytopenia (43%), fatigue (16%), and neutropenia (11%). Supportive care, including granulocyte colony stimulating factors, thrombopoietin receptor agonists, optimization of fluid and caloric intake, appetite stimulants, psychostimulants and/or additional anti-nausea agents usually reduced the intensity and/or duration of AEs. Side effects were reversible without evidence of toxic effects in major organs (treatment-related cardiac, pulmonary, hepatic, or renal dysfunction of Grade 3 or higher) or cumulative toxic effects, with irreversible acute kidney injury reported in one patient (1%). Serious AEs occurred in 63% of patients, with pneumonia (11%) and sepsis (9%) being the most common. Twenty-eight patients died during the study: 16 from disease progression and 12 from an AE. Of these 12 patients, two were assessed by the investigator as related to treatment (one patient having pneumonia with concurrent disease progression and the other having sepsis).

The complete results of this study were published in the *New England Journal of Medicine*. However, the FDA's accelerated approval of XPOVIO was based upon the efficacy and safety in a pre-specified sub-group 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 overall response rate in this patient population was 25.3%.

Additional data and analysis from the STORM study were also presented at key medical conferences in 2019 including the European Hematology Association, or EHA, the International Myeloma Working Group, or IMWG, and the American Society of Hematology, or ASH, annual meetings.

The Phase 1b/2 STOMP Study

The STOMP study, a multi-arm clinical trial in patients with multiple myeloma, is evaluating selinexor and low-dose dexamethasone plus standard therapies, such as Velcade, Kyprolis, Revlimid, Pomalyst or Darzalex. An additional arm of the study evaluating selinexor in combination with Revlimid in patients with previously untreated myeloma was opened in June 2018. We presented updated clinical data from the STOMP study at both the EHA 2019 annual meeting in June 2019 as well as at the ASH 2019 annual meeting in December 2019 demonstrating that selinexor and low-dose dexamethasone plus standard anti-myeloma therapies exhibit encouraging response rates when combined with these approved therapies.

Selinexor plus Pomalyst and Low-dose Dexamethasone (SPd) Presented at the ASH 2019 Annual Meeting

In this all oral arm of the Phase 1b/2 STOMP study, oral selinexor (60-100mg weekly or 40-80mg twice weekly) is being evaluated in combination with Pomalyst (3 or 4mg orally, once daily) and low dose dexamethasone (orally, 40mg once weekly or 20mg twice weekly) in patients with relapsed or refractory multiple myeloma who received at least three prior lines of therapy, including a PI and an IMiD, or patients with myeloma refractory to both a PI and an IMiD. The following table is a summary of the interim efficacy data:

Best Responses ¹ in Evaluable SPd Patients as of 1-Oct-2019 ²					
Prior Therapy Status	N ³	ORR	VGPR ⁴	PR	Median PFS
Pomalyst-naïve and Revlimid refractory or relapsed	32	18 (56%)	6 (19%)	12 (38%)	12.2 months
Pomalyst Treated and Revlimid refractory	14	5 (36%)	1 (7%)	4 (29%)	5.6 months

Key: ORR=Overall Response Rate (VGPR+PR); VGPR=Very Good Partial Response; PR=Partial Response

¹ Responses were adjudicated according to the International Myeloma Working Group criteria

² Based on interim unaudited data

³ Five patients not evaluable for response: one death unrelated to myeloma, one non-compliance with study procedures, one withdrawal of consent before disease follow up, one death related to progressive disease, or PD; one PD before completing one cycle of therapy

⁴ One unconfirmed VGPR

Among the patients evaluated for safety as of the data cutoff date, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms; most were manageable with dose modifications and/or supportive care. The most common non-hematologic treatment-related AEs were nausea (52%), fatigue (52%) and weight loss (39%). As expected, the most common treatment-related Grade 3 and 4 AEs were neutropenia (58%), thrombocytopenia (27%) and anemia (27%).

Selinexor plus Kyprolis and Low-dose Dexamethasone (SKd) Presented at the ASH 2019 Annual Meeting

In this arm of the Phase 1b/2 STOMP study, oral selinexor (80 or 100mg once-weekly) is being evaluated in combination with Kyprolis (56mg/m² or 70mg/m² once weekly) and low dose dexamethasone (orally, 40mg once weekly or 20mg twice weekly) in patients with relapsed refractory multiple myeloma who have received at least two prior therapies, which can include previous treatment with a PI, one or more IMiDs or Darzalex. The median number of prior treatments was four (with a range of two to eight). The following table is a summary of the interim efficacy data:

Best Responses ¹ in Evaluable SKd Patients as of 1-Oct-2019 ²					
Category	N	ORR	CR	VGPR	PR
All (Kyprolis-naïve)	14	10 (71%)	3 (21%)	7 (50%)	—

Key: ORR=Overall Response Rate (CR+VGPR+PR); CR=Complete Response; VGPR=Very Good Partial Response; PR=Partial Response

¹ Responses were adjudicated according to the International Myeloma Working Group criteria

² Based on interim unaudited data

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All patients had reductions in myeloma protein, or M-protein, from baseline, with 71% of patients experiencing a reduction of 90% or more. As of the data cutoff date, median PFS had not yet been reached.

Among the patients evaluated for safety, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms; most were manageable with dose modifications and/or supportive care. The most common non-hematologic treatment-related AEs were nausea (71%), fatigue (43%), anorexia (36%), vomiting (36%) and weight loss (36%) and were mostly Grade 1 and 2 events. As expected, the most common treatment-related Grade ≥ 3 AEs were hematologic AEs and included thrombocytopenia (64%), anemia (14%) and leukopenia (14%). The recommended Phase 2 dose, or RP2D, was identified as selinexor 80mg and Kyprolis 56mg/m² and enrollment continues using this regimen.

Selinexor plus Revlimid and Low-dose Dexamethasone (SPd) in Newly Diagnosed Patients with Multiple Myeloma Presented at the ASH 2019 Annual Meeting

In this all oral arm of the Phase 1b/2 STOMP study in patients with newly diagnosed multiple myeloma, selinexor (60mg orally once-weekly) is being combined with Revlimid (25mg orally, once daily) and low dose dexamethasone (orally, 40mg once weekly or 20mg twice weekly). The following table is a summary of the interim efficacy data:

Best Responses ¹ in Evaluable SRd Patients as of 1-Oct-2019 ²					
Category	N ³	ORR	CR	VGPR ⁴	PR
All	7	6 (86%)	1 (14%)	4 (57%)	1 (14%)

Key: ORR=Overall Response Rate (CR+VGPR+PR)

¹ Responses were adjudicated according to the International Myeloma Working Group criteria

² Based on interim unaudited data

³ One patient was not evaluable for response due to withdrawn consent prior to disease follow-up

⁴ One VGPR was confirmed on Oct 10, 2019 (after data cut); two VGPR are unconfirmed

The data are early and the median PFS was not reached. Among the 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 supportive care. The most common non-hematologic treatment-related AEs were diarrhea (63%), weight loss (63%), nausea (50%), constipation (38%), fatigue (38%), hypokalemia (38%) and insomnia (38%) and were mostly Grades 1 or 2. The most common Grade ≥ 3 AEs were neutropenia (75%), anemia (50%) and thrombocytopenia (25%). Among the five patients evaluable for dose limiting toxicities, or DLTs, as of the data cutoff date, there were no DLTs observed.

Selinexor plus Darzalex and Low-dose Dexamethasone (SDd) Presented at the EHA 2019 Annual Meeting

In this arm of the Phase 1b/2 STOMP study, oral selinexor (dose escalated using either 100mg once weekly or 60mg twice weekly) is being evaluated in combination with Darzalex (16mg/kg intravenously once weekly) and low dose dexamethasone (orally, 40mg once weekly or 20mg twice weekly) in patients with relapsed or refractory multiple myeloma who received at least three prior lines of therapy, including a PI and an IMiD, or patients with multiple myeloma refractory to both a PI and an IMiD. The following table is a summary of the updated interim efficacy data:

Best Responses ¹ in Evaluable SDd Patients as of 1-May-2019 ²				
Category	N ³	ORR	VGPR	PR ⁴
Darzalex naïve	30	22 (73%)	11 (37%)	11 (37%)
All	32	22 (69%)	11 (34%)	11 (34%)

Key: ORR=Overall Response Rate (VGPR+PR); PR= Partial Response

¹ Responses were adjudicated according to the International Myeloma Working Group criteria

² Based on interim unaudited data

³ Two patients were not evaluable for response as they withdrew consent prior to disease follow up

⁴ Two unconfirmed PRs

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Despite the heavily pretreated nature of the patients in the study, with 100% of the patients having disease refractory to both a PI and an IMiD, only one patient (3%) did not have at least a minimal response. As of the data cutoff date, median PFS had not been reached. Among patients with at least a PR, the median time on treatment was 7.7 months, while the median time on study for all evaluable patients was 4.8 months. Median time to response was 1.0 month. Based on published data, the expected ORR for Darzalex therapy without selinexor in the PI- and IMiD-refractory, Darzalex-naïve population is approximately 29%, and the anticipated response rate with selinexor-dexamethasone in this population is $\leq 30\%$ based on the STORM and previous studies. Thus, the ORR of 73% continues to provide a basis for further evaluation of the SDD combination. Among the 31 patients evaluated for safety, the most common treatment-related AEs were cytopenias, along with gastrointestinal and constitutional symptoms; most were manageable with dose modifications and/or supportive care. The most common non-hematologic treatment-related AEs were nausea (68%), fatigue (58%), anorexia (32%), insomnia (32%), diarrhea (32%), hyponatremia (32%), and vomiting (26%) and were mostly Grade 1 and 2 events. As expected, the most common Grade 3 and 4 treatment-related AEs were hematologic AEs and included thrombocytopenia (42%), anemia (29%), leukopenia (26%) and neutropenia (23%). Based on these tolerability and efficacy data, the recommended RP2D of SDD is selinexor (100mg orally, once weekly), Darzalex (16mg/kg, once weekly) and dexamethasone (40mg orally, once weekly).

Selinexor plus Velcade and Low-dose Dexamethasone (SVd) Published in Blood 2018

In this arm of the Phase 1b/2 STOMP study, oral selinexor was studied in 42 patients who received selinexor (60, 80, or 100mg orally, once or twice weekly) plus Velcade (1.3mg/m² subcutaneously) and dexamethasone (20mg orally) once or twice weekly in 21- or 35-day cycles. In the dose-escalation phase, patients were randomized to one of two treatment cohorts to receive selinexor once weekly or twice weekly in 21- or 35-day cycles, depending on the bortezomib dosing schedule. Based on long-term tolerability and efficacy, the recommended RP2D of SVd was established at 100 mg selinexor once weekly plus 40 mg dexamethasone once weekly and 1.3 mg/m² bortezomib once weekly in 35-day cycles.

Patients had a median of three prior lines of therapy (with a range of one to 11), and 50% were refractory to a PI. Treatment-related Grade 3 or 4 AEs reported in $\geq 10\%$ of patients were thrombocytopenia (45%), neutropenia (24%), fatigue (14%), and anemia (12%). The incidence and severity of peripheral neuropathy were low, with four (10%) patients experiencing this AE at a grade limited to two or below. The ORR for the entire population was 63% with an 84% ORR for patients with disease that was not refractory to a PI and 43% in patients with disease refractory to a PI. The median PFS for all patients was 9.0 months; 17.8 months for PI-nonrefractory, and 6.1 months for PI-refractory.

The results from the SVd arm of the STOMP study were published in the journal *Blood* (2018 Dec 13; 132(24): 2546–2554). The SVd arm of the STOMP study served as the basis for the design of the Phase 3 BOSTON study evaluating once-weekly selinexor, once-weekly Velcade and dexamethasone in patients who have had one to three lines of prior multiple myeloma therapy.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma, or NHL, is 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 United States, accounting for about 4% of all cancers. In 2020, the American Cancer Society, or ACS, estimates that more than 77,000 patients will be diagnosed with NHL and nearly 20,000 deaths will result from the disease. DLBCL is the most common and the most aggressive of the different forms of NHL, making up approximately 18,000 of the new cases diagnosed annually in the United States. Approximately 50% of newly diagnosed patients are currently cured with front-line (typically "R-CHOP" chemotherapy) and another approximately 10% of patients are cured with second line intensive chemotherapy followed by autologous stem cell transplantation. The remaining patients generally succumb to the disease, with the median OS of patients with relapsed or refractory

DLBCL after two prior regimens less than one year, and often less than six months. Despite the recent approval of CAR-T therapy, many patients with relapsed/refractory DLBCL are not medically stable enough to undergo CAR-T therapy. The FDA recently granted accelerated approval to the triplet therapy polatuzumab vedotin, bendamustine, rituximab, known as PBR, for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified after at least two prior therapies.

The Phase 2b SADAL Study

The SADAL study is an open-label Phase 2b clinical trial evaluating single-agent oral selinexor (60mg, twice weekly) in patients that have relapsed or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. At the ASH 2018 annual meeting, we presented top-line clinical data from the SADAL study demonstrating that selinexor, when administered as a single-agent, is clinically active and capable of producing durable responses associated with prolonged overall survival. Updated data were presented at the 2019 International Conference on Malignant Lymphoma, or ICML, meeting on June 19, 2019. The results presented at the ICML meeting remain consistent with those reported at the ASH 2018 annual meeting and include efficacy results from the final 12 patients who had not reached their first response assessment in time to be included in the previously released top-line efficacy analyses. Among the 127 patients (median of two prior treatment regimens with a range one to six) who were evaluable for response, as adjudicated by an Independent Central Radiological Review, or ICRR, committee, 36 patients responded (13 CRs and 23 PRs) for an ORR of 28.3%. An additional 11 patients experienced stable disease, or SD, for a disease control rate, or DCR, of 37.0%. Selinexor also demonstrated responses in patients with either GCB or non-GCB subtypes of DLBCL: the ORR in the 59 patients with the GCB-subtype was 33.9% and the ORR in the 63 patients with the non-GCB subtype was 20.6%. In addition, there were five patients enrolled whose subtype was unclassified and one of these patients achieved a CR while two of these patients achieved a PR.

The median DOR across responding patients was 9.2 months and responses tended to occur rapidly, with most documented at the first post-baseline radiological evaluation (weeks 8-9). Median OS for the entire patient population was 9.0 months while median OS has not yet been reached in patients who achieved either a CR or PR. Patients whose disease progressed or had no response to selinexor had a median OS of 4.1 months, which is consistent with the expected poor prognosis (OS <six months) for patients who have relapsed or refractory DLBCL and have been previously treated with two or more lines of therapy.

All 127 patients were included in the safety analyses. The most common treatment-related AEs were cytopenias along with gastrointestinal and constitutional symptoms and were generally reversible and most were manageable with dose modifications and/or supportive care. The most common non-hematologic AEs were nausea (52.8%), fatigue (37.8%), and anorexia (34.6%) and were mostly Grade 1 and 2 events. As expected, the most common Grade 3 and 4 AEs were thrombocytopenia (39.4%), neutropenia (20.5%) and anemia (13.4%) and were generally not associated with clinical sequelae.

In November 2018, the FDA granted Fast Track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. Selinexor has also been granted Orphan Drug designation by the FDA in DLBCL. Based on the positive results of the SADAL study, we submitted an sNDA to the FDA on December 23, 2019, with a request for accelerated approval for selinexor as a new treatment for adult patients with relapsed or refractory DLBCL, not otherwise specified, who have received at least two prior therapies. The FDA filed the application on February 18, 2020 and granted Priority Review with a target decision date of June 23, 2020 under PDUFA. We also plan to submit a MAA to the EMA in 2020 with a request for conditional approval.

We plan to initiate two studies in DLBCL during 2020. XPORT-DLBCL-030, which is expected to serve as a confirmatory study for the accelerated approval requested in DLBCL based on the SADAL study, is a Phase 3 trial of selinexor or matching placebo given with the standard combination immunochemotherapy R-GDP

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(rituximab, gemcitabine, dexamethasone, cisplatin) to patients with at least one prior therapy and who are ineligible for high dose chemotherapy and stem cell transplantation (or CAR-T). The primary endpoint of the study is PFS, and this study is expected to initiate in mid-2020. XPORT-DLBCL-025 is a multi-arm study of selinexor in combination with commonly used and approved agents for the treatment of DLBCL; this study is expected to begin in the second half of 2020. This study will inform the use of selinexor with a variety of additional agents for the treatment of DLBCL.

Advanced or Metastatic Solid Tumors

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 SD with disease control greater than three months. Our Phase 1b study in patients with liposarcoma and other sarcomas demonstrated durable SD with single agent selinexor, and our Phase 2 studies of selinexor in gynecological malignancies and glioblastoma multiforme, or 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 like liposarcoma and endometrial cancer with plans to expand development in GBM, and to advance combination therapy development with both standard of care and emerging therapies like immune checkpoint inhibitors.

Liposarcoma

Liposarcoma represents an area of high unmet need, with currently approved treatments for aggressive disease limited to parenteral chemotherapies. Liposarcoma arises from fat cells or their precursors and represents up to 18% of all soft tissue sarcoma, or approximately 2,500 new cases per year in the United States. Liposarcoma most commonly occurs in the thigh, behind the knee, the groin, the gluteal area or behind the abdominal cavity. 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 Phase 2/3 SEAL Study in Liposarcoma

In our Phase 1b trial to evaluate the effects of food and formulation on selinexor pharmacokinetics in patients with soft tissue or bone sarcoma, 31 of 54 sarcoma patients (57%) experienced SD with single agent selinexor treatment. Fifteen of the 54 patients had dedifferentiated liposarcoma. Of these 15 patients with dedifferentiated liposarcoma, 13 (87%) experienced SD and seven (47%) experienced SD of four months or longer.

In light of the Phase 1b data, we are conducting the SEAL (**S**elinexor in **A**dvanced **L**iposarcoma) study, a multi-center, randomized, double-blind, placebo-controlled Phase 2/3 clinical trial evaluating single-agent oral selinexor in patients with advanced unresectable dedifferentiated liposarcoma who received at least one line of prior systemic therapy. Patients are randomized to receive either 60mg of selinexor or placebo, respectively, each given twice weekly until progression or intolerability. Patients on placebo with confirmed progressive disease are permitted to cross over to the selinexor treatment arm. In June 2018, we reported a successful outcome from the Phase 2 portion of the SEAL study of 56 patients with previously treated, advanced unresectable dedifferentiated liposarcoma. The median number of prior treatment regimens was two (range of two to 10 prior treatment regimens). For the study's primary endpoint, patients treated with selinexor achieved PFS of 5.5 months, compared to 2.7 months for placebo-treated patients with a hazard ratio of 0.67, representing a 33% reduction in

the risk of progression or death. PFS was assessed by an ICRR committee based on RECIST v1.1. In this randomized, blinded Phase 2 portion of the study, selinexor demonstrated a safety and tolerability profile consistent with prior studies with AEs, primarily consisting of nausea, fatigue, anorexia and weight loss, and low levels of Grade 3/4 cytopenias, and no new or unexpected safety signals were identified. The majority of treatment-related AEs were low grade and reversible with dose modifications and/or supportive care. The data from the Phase 2 portion of the SEAL study, which is complete, demonstrate that treatment with selinexor improves PFS (based on the RECIST v1.1 criteria) and supports the currently ongoing Phase 3 portion of the study using RECIST v1.1 response criteria, and for which top-line data are anticipated in 2020.

The Phase 3 portion of the SEAL study is being conducted in North America and Europe. In this blinded, placebo-controlled Phase 3 study, patients are randomized 2:1 to receive either oral selinexor (60mg twice weekly) until disease progression or intolerability, or placebo. Patients whose disease progresses on placebo will be permitted to cross over to the selinexor arm. The primary endpoint of the Phase 3 portion of the study is PFS as assessed by the ICRR committee based on RECIST v1.1. The Phase 3 study design and primary endpoint of PFS were agreed to by the FDA. Top-line data from the Phase 3 portion of the SEAL study are anticipated in 2020. Assuming a positive outcome, these data are intended to support regulatory submissions requesting approval for oral selinexor as a new treatment for patients with advanced unresectable dedifferentiated liposarcoma. Selinexor received Orphan Drug designation by the FDA for the patient population being evaluated in the SEAL study.

Endometrial Cancer

Endometrial cancer, also called endometrial carcinoma, occurs when cells in the endometrium, which is the inner lining of uterus, begin to grow out of control. In the United States, endometrial cancer is the most common cancer of the female reproductive organs. The NCI estimates that approximately 62,000 new cases of endometrial cancer will be diagnosed in 2020, with approximately 12,000 deaths. Endometrial cancer affects mainly post-menopausal women and the average age of a women diagnosed with endometrial cancer is 60.

The Phase 2/3 SIENDO Study in Endometrial Cancer

SIENDO is a randomized, blinded Phase 2/3 trial evaluating 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. During the first quarter of 2019 an Investigational New Drug, or IND, application was submitted by us and accepted by the FDA, resulting in the transition of this study from investigator-sponsored to company-sponsored. The overall objective of SIENDO is to obtain conclusive evidence of efficacy for maintenance selinexor in patients with advanced or recurrent endometrial cancer. This is a multi-national, multi-center trial and is expected to enroll approximately 192 patients. We currently expect to report topline data from the SIENDO study in 2021.

This trial was designed based on the data from our SIGN study, a Phase 2, open-label study of efficacy and safety of oral selinexor in patients with heavily pre-treated, progressive gynecological cancers. In December 2019, the full results from the SIGN study in patients with recurrent gynecological malignancies were published in *Gynecologic Oncology* (I.B. Vergot et.al., *Gynecologic Oncology*. December 2019). 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 7 patients (11%) with a PR. The median duration of response 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

Glioblastoma multiforme, or GBM, is an area of high unmet need, with existing treatments having very limited success in increasing overall surviving rates. GBM is the most common and aggressive malignant primary brain tumor in humans, accounting for 60% of brain tumors in adults. Patients facing GBM face significant morbidity and mortality rates, with over 13,000 deaths per year in the United States. Additionally, GBM patients endure poor prognosis rates, with a 1-year survival rate of 37.2%, a 5-year survival rate of 5.1%, and a median survival rate of roughly 10 months. The current standard of care for GBM patients includes surgery, radiation therapy, and chemotherapy. 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.

The Phase 2 KING Study in Glioblastoma Multiforme

The KING study is a Phase 2 study evaluating the efficacy and safety of oral selinexor in patients with recurrent GBM. In June 2016, we presented data at the American Society of Clinical Oncology, or ASCO, annual meeting where we showed that single-agent oral selinexor demonstrated anti-tumor activity in patients with glioblastoma that recurred after temozolomide and radiation therapy, including selinexor brain penetration at clinically relevant levels, leading to durable anti-cancer activity and disease control of up to 6 months. Specifically, data as of May 23, 2016 from 33 surgically ineligible patients with GBM that progressed after treatment with temozolomide and radiation showed that selinexor dosed twice weekly at 50mg/m² (or approximately 80mg flat dosing) demonstrated anti-tumor activity with a 12% ORR (PR or better) and a 33% DCR (SD or better) with durability of up to six months in two patients. The most common AEs were thrombocytopenia, fatigue, anorexia, and nausea, consistent with the selinexor adverse event profile.

In July 2019, updated data were presented at the ASCO 2019 annual meeting based on 76 total patients enrolled in the study as of May 2019. While multiple doses of selinexor were tested in this study (50mg twice weekly, 60 mg twice weekly and 80mg once weekly), the dose of 80mg once per week was determined to be the recommended dose for further evaluation. In the study, there were 30 patients treated with selinexor 80 mg once per week. In this cohort, the rate of patients who were still alive and did not have their disease progress after six 28-day cycles on therapy (called the six-cycle PFS rate) was 30%, the rate of patients who were still alive and did not have their disease progress after six months on therapy (called the six-month PFS rate) was 19%, and the ORR was 10%. Additionally, the median OS in this arm of the trial was 9.4 months. The most common AEs in this arm of the trial were nausea, fatigue, anorexia, leukopenia, and neutropenia and were predominately Grade 1 and 2 adverse events. No Grade 4 treatment-related AEs were reported in ≥ 10% of patients and no fatal (Grade 5) treatment-related AEs were reported.

The Phase 1/2 XPORT-GBM-029 Study in GBM

Based on these positive findings from the KING study, during the second half of 2020, we plan to initiate XPORT-GBM-029, a new Phase 1/2 multi-center, open-label study to evaluate selinexor in combination with standard of care therapies. The Phase 1 portion of the study is expected to evaluate selinexor in combination with radiation with or without temozolomide in newly diagnosed GBM and selinexor in combination with lomustine chemotherapy in recurrent GBM. The Phase 2 portion of the study is designed to be a randomized study to compare the combinations evaluated in the Phase 1 portion against standard of care therapies alone in patients with recurrent or newly diagnosed GBM.

Our Other Pipeline Programs

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 believed to be the same as selinexor.

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Eltanexor differs from selinexor primarily because it was designed and confirmed to have much lower penetration into the brain in preclinical species compared with selinexor. Following oral administration, animals treated with eltanexor show 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 more frequent dosing of eltanexor, enabling a longer period of exposure at higher levels than is possible with selinexor, which allows for greater indication diversification among our SINE compounds. In many preclinical model systems, the more intensive dosing regimen leads to superior efficacy in comparison to selinexor treatment. Therefore, eltanexor may cause fewer side effects which are believed to be mediated through the central nervous system such as nausea, fatigue and anorexia in humans. As a result, we believe that eltanexor represents a second-generation SINE compound and are evaluating safety, tolerability and efficacy in humans.

We initiated our first-in-humans Phase 1/2 clinical trial for eltanexor in patients with relapsed/refractory multiple myeloma in January 2016. At the ASH 2017 annual meeting, we reported positive data from the ongoing Phase 1/2 study demonstrating good tolerability and promising activity in multiple myeloma. The median time on treatment for the overall study population was greater than 130 days, with a range of 10 days to over two years. The ORR across all 34 patients was 21% including one patient with VGPR. No CRs were observed. Among the 14 patients who received a starting dose of eltanexor in combination with dexamethasone, the ORR was 35.7%.

Among the 39 patients evaluable for safety, the most common Grade 1/2 AEs in the multiple myeloma patient population were nausea (54%), fatigue (46%), anemia (38%), diarrhea (38%), dysgeusia (33%), weight loss (33%) and neutropenia (31%). As expected in this patient population, the most common Grade 3/4 AEs were thrombocytopenia (56%), neutropenia (26%), anemia (15%), leukopenia (15%) and hyponatremia (10%). Importantly, nausea, fatigue, diarrhea and vomiting were nearly all Grade 1, generally manageable and transient, and bleeding was uncommon. The maximum tolerated dose was not reached; however, dose escalation was halted as responses were achieved. Based on these data, the RP2D in this patient population has been established as 20mg eltanexor dosed five times per week with 20mg dexamethasone dosed twice weekly.

This Phase 1/2 study has been expanded to include patients with high risk MDS, metastatic CRC or metastatic CRPC to determine the safety, preliminary efficacy, and RP2D of eltanexor in patients with these advanced cancers. These are indications where selinexor and XPO1 inhibition has shown clear activity, but where side effects such as fatigue and anorexia were problematic for patients due to the underlying malignancies.

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 (10mg or 20mg once-daily for five days per week) in elderly patients with higher-risk MDS with disease refractory to hypomethylating agents. Of the 20 patients evaluable for efficacy, seven patients had a complete response without marrow recovery, or mCR, indicating an ORR of 35%. An additional five patients (25%) achieved SD as their best response. Median OS 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 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 either amend the existing Phase 1/2 study protocol or implement a new protocol to evaluate eltanexor in combination with cedazuridine-decitabine (ASTX727) in patients with newly diagnosed MDS. The dose finding portion of the study evaluating this novel combination is expected to begin during the second half of 2020. Once the RP2D of this combination is established, the study is expected to expand into a Phase 2/3 study to explore the efficacy of this combination in newly diagnosed MDS.

KPT-9274

KPT-9274 is a first-in-class orally bioavailable small molecule that is a non-competitive dual modulator of p21-activated kinase 4, or PAK4, and nicotinamide phosphoribosyltransferase, or NAMPT, which is also known

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as PBEF or visfatin. Co-inhibition of these targets leads 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 become dependent on both PAK4 and NAMPT pathways and are therefore susceptible to single-agent cytotoxic effect 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, KPT-9274 given orally has shown evidence of anti-cancer activity and tolerability. To our knowledge, we are the only company with an allosteric, PAK4 and/or NAMPT specific inhibitor currently in clinical development.

We initiated a first-in-humans Phase 1 open-label clinical trial evaluating the safety, tolerability, and efficacy of KPT-9274 in patients with advanced solid malignancies or non-Hodgkin's lymphoma. Top-line results from this Phase 1 study were presented in September 2017 at the European Society of Medical Oncology, or ESMO, annual meeting. Among the 18 patients evaluable for preliminary efficacy, there were six (33%) with SD, the longest for 7.3 months. Tumor reductions were observed in three out of three patients with NAPRT1 deficient tumors. Among the 21 patients evaluated for safety, the most common Grade 2 AEs across dose levels were arthralgia (43%), anemia (24%) and fatigue (24%). The most common drug-related Grade 3 or higher AEs across dose levels include anemia (38%) and fatigue (5%). Gastrointestinal-related AEs were infrequent and low grade. In addition, it was determined that niacin can be safely administered with KPT-9274 and may improve tolerability, particularly with respect to anemia. Dose escalation remains ongoing and further evaluation of effects in NAPRT1 deficient tumors is planned. Enrollment is planned to continue based on the patients' NAPRT1 status in a 2:1 ratio with twice as many patients with negative NAPRT1 enrolled versus those patients with positive NAPRT1. These study findings indicate that in patients whose disease has progressed despite most available therapies, KPT-9274 can induce tumor shrinkage and disease stabilization.

In addition, we plan to evaluate the combination of KPT-9274 with an anti-PD1 monoclonal antibody in a phase 1 clinical study in the near future.

Verdinexor (KPT-335): Oral SINE Compound for 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 display a comparable genetic profile and respond to chemotherapy in a fashion similar to their human counterparts (human NHL, most closely DLBCL). Lymphomas are one of the most common tumors in pet dogs. Lymphoma in dogs is very aggressive and, without treatment, the tumors are often fatal within weeks. The majority of dog 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 (KPT-335), a closely related, orally available SINE compound in pet dogs with lymphomas. Verdinexor received a Minor Use / Minor Species, or MUMS, designation from the FDA's Center for Veterinary Medicine, or CVM, for the treatment of newly-diagnosed or first relapse after chemotherapy lymphomas in pet dogs.

Several different dog tumor cell lines, including those derived from lymphomas, exhibited growth inhibition and apoptosis in vitro upon exposure to nanomolar concentrations of verdinexor. Data from a Phase 1 clinical trial of verdinexor as well as dose expansion study involving pet dogs with cancer, primarily with lymphoma, show efficacy of verdinexor to treat dogs with lymphoma. Side effects included anorexia, weight loss, vomiting and diarrhea and were manageable with dose modulation and supportive care. We conducted an owner observation-based survey and the data indicated that the overall quality of life did not change significantly in dogs treated with verdinexor. Based on these findings, a Phase 2b clinical trial, intended to support regulatory approval under the MUMS designation in the United States, was performed in 58 pet dogs with either newly-diagnosed or first relapse after chemotherapy lymphomas. Verdinexor was administered initially at doses ranging from 25mg/m² to 30mg/m² two or three days per week. Minimal or no supportive care was given. The results of

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this Phase 2b clinical trial were published in *BMC Veterinary Research* (Sadowski, A.R., et.al., August 2018). According to the published data, the ORR among the 58 dogs was 37%. The most common AEs related to verdinexor included anorexia, weight loss, vomiting, lethargy and diarrhea. Most events (95%) were considered grade 1 or 2. We submitted the safety and effectiveness sections of a New Animal Drug Application for verdinexor to the CVM in December 2013.

In May 2017, we entered into an exclusive licensing agreement with Anivive Lifesciences, Inc., or 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 exchange, we received an upfront payment and are eligible to receive future milestone payments and royalties. If approved, we believe that verdinexor would represent the first non-chemotherapy-based approval for the treatment of dog lymphoma.

The Potential of XPO1 in Settings Beyond Oncology

In addition to its role in cancer, XPO1 is known to play a role in neurological, inflammatory, viral, wound healing and other diseases. In the hands of academic collaborators, SINE compounds have shown activity in a variety of non-oncology models consistent with the biology of XPO1. In January 2018, we entered into an Asset Purchase Agreement with Biogen MA Inc., a subsidiary of Biogen Inc., or Biogen, pursuant to which Biogen acquired KPT-350, an investigational new drug 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, or ALS. According to publicly available information, an IND application for KPT-350 (now BIIB100) was filed in December 2018 and the first patient was dosed in a Phase 1 study of sporadic ALS in June 2019.

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.

Our Non-Oncology Drug Candidates

Verdinexor (KPT-335): Oral SINE Compound for Viral, Rare Disease and Autoimmune Indications

Verdinexor (KPT-335) is an oral SINE compound and our lead compound that is being evaluated as a potential therapy for viral, inflammatory, and autoimmune indications, in addition to the canine lymphoma program described above. Several autoimmune indications are driven by aberrant pro-inflammatory responses, particularly uncontrolled pro-inflammatory cytokine expression and NF- κ B activation. These include systemic lupus erythematosus, or SLE, a primary focus of our work with verdinexor. Funded by a grant under the Small Business Innovation Research program, the work to complete pre-clinical evaluation of verdinexor as a treatment for SLE is expected to finish in early 2020. At such time, we expect to be in position to file an IND application with the FDA. In addition to SLE, we are initiating preclinical research in spinal cord injuries. In September 2019, we and our collaborator were awarded \$2.1 million in grant funding from the U.S. Department of Defense to cover all preclinical work required to reach IND-readiness in the field of spinal cord injuries.

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. We intend to extend preclinical research in viruses that may be relevant to patients with compromised immune systems, such as cytomegalovirus, or CMV. As such, we are conducting pre-clinical animal studies of verdinexor in CMV-infected mice with the National Institutes of Health. We also intend to investigate verdinexor to treat inflammation in virally-suppressed antiretroviral therapy-receiving individuals.

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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. 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 a collaborator or through government-funded grant or contract opportunities.

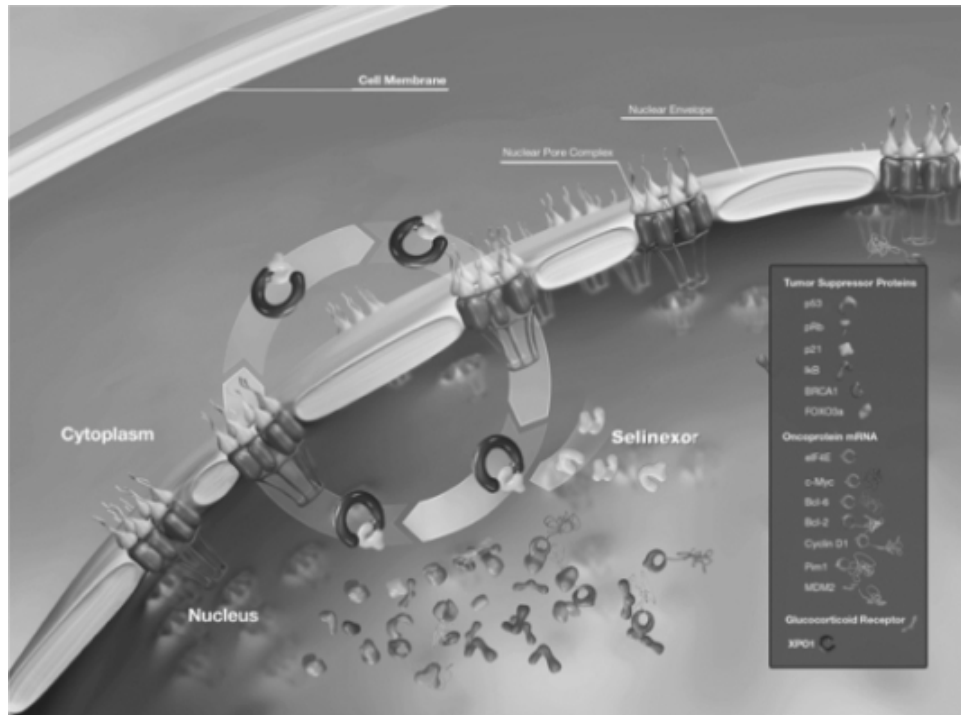
As part of the exclusive license agreement we entered into with Antengene Therapeutics Limited, or Antengene, in May 2018, we granted Antengene exclusive rights to develop and commercialize verdinexor for the diagnosis, treatment and/or prevention of certain human non-oncology indications in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

Summary of Mechanism of Action: Transient XPO1 Inhibition by SINE Compounds

Certain functions may only occur within a particular location in the cell, so one of the ways a cell regulates the function of a particular protein is by controlling that protein's location within the cell. 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 export of over 220 mammalian cargo proteins and some growth-promoting mRNAs. Particularly, XPO1 mediates the transport of the majority of tumor suppressor proteins and appears to be the only mediator of nuclear export for these proteins. Cancer cells have increased levels of XPO1, causing the increased export of these tumor suppressor proteins from the nucleus. Since the tumor suppressor proteins must be located in the nucleus to survey for DNA damage and initiate programmed cell death, or apoptosis, XPO1 overexpression in cancer cells neutralizes their tumor suppressing function by removing them from the nucleus. By blocking XPO1, our SINE compounds inhibit the export of tumor suppressor proteins, leading to their accumulation and functional reactivation in the nucleus. The accumulation of tumor suppressor proteins in the nucleus amplifies their natural apoptotic function in cancer cells. Because normal cells have little or no DNA damage, accumulation of tumor suppressor proteins in their nucleus generally does not lead to apoptosis. Further, SINE compounds reduce the translation of certain growth-promoting and anti-apoptosis proteins—often called oncoproteins—by inhibiting the XPO1-mediated nuclear to cytoplasmic transport of a protein called eIF4E (eukaryotic protein translation initiation factor 4E), which itself binds to the

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mRNAs that code for these proteins. 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 the XPO1-inhibiting SINE compounds that we have discovered and developed to date, including selinexor, have the potential to provide novel, oral, targeted therapies that enable tumor suppressor proteins to remain in the nucleus and promote the apoptosis of potentially any type of cancer cell. In multiple cancer types, patient tumor biopsies have confirmed that selinexor treatment induces nuclear localization of tumor suppressor proteins and, subsequently, cancer cell death, or apoptosis. We believe that XPOVIO is the only currently approved cancer treatment selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus. We believe that selinexor's novel mechanism of action and oral administration and low levels of major organ toxicities observed to date in patients treated with selinexor in clinical trials, along with encouraging efficacy data, support the potential for selinexor's broad use across many cancer types, including both hematological and solid tumor malignancies. Our SINE compounds were the first oral XPO1 inhibitors in clinical development. We own all intellectual property rights related to the compounds that we are developing, including composition of matter and method of use patents covering selinexor issued by the U.S. Patent and Trademark Office in 2015 and which provide patent protection through at least 2032, prior to any adjustments or extensions.

Our Strategy

The critical components of our business strategy are to:

- **Maximize the Commercial Value of XPOVIO and Our Other Drug Candidates.** We are also executing on our U.S. commercial capabilities and supporting the ongoing launch of XPOVIO in the United States. In 2019 we launched XPOVIO in the U.S. market. As of December 31, 2019, approximately 1,400 XPOVIO prescriptions had been fulfilled, driven by strong demand from both academic and community-based oncologists, and XPOVIO had been prescribed by more than 550

unique physicians and healthcare accounts. In 2020, we plan to further penetrate the U.S. commercial market and further educate the medical community about the clinical data that supported the accelerated approval of XPOVIO. Outside of the United States, we will either work with existing and potential partners to establish such commercial infrastructure or may consider establishing this infrastructure ourselves on a case by case basis. To date, we have entered into several strategic arrangements. In October 2017, we entered into an exclusive license agreement with Ono Pharmaceutical Co., Ltd. for the development and commercialization of selinexor and eltanexor for all human oncology indications in Japan, South Korea, Taiwan, Hong Kong, and the ASEAN countries. In May 2018, we entered into an exclusive license agreement with Antengene under which we granted Antengene exclusive rights to develop and commercialize 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. We licensed the development and commercial rights to Antengene for selinexor and eltanexor in the oncology field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the oncology field and verdinexor in the non-oncology field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. We currently hold development, marketing, and commercialization rights for selinexor in all other countries and are developing selinexor and seeking regulatory approval for its use in oncology indications without a collaborator in North America and Europe.

- **Continue to Develop and Seek Regulatory Approvals of Selinexor, Our Lead Novel Drug Candidate, in North America and Europe.** We plan to seek regulatory approvals of selinexor in North America and Europe for each indication in which we receive favorable results in a trial with a survival endpoint that is registration-enabling. As we did with XPOVIO based on results of the STORM study, we may also seek regulatory approvals where a clinical trial demonstrates significant data in a surrogate endpoint, such as overall response rate, that could allow for accelerated or conditional approval. We or our current or future partners may seek marketing approvals in other geographies as well.
- **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 major 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. One such example includes the recently initiated combination study of selinexor with Venclexta[®] (venetoclax), an oral inhibitor of the oncoprotein bcl-2. Pre-clinical studies have suggested that the combination may be synergistic in killing cancer cells and a new investigator-sponsored study at Vanderbilt University was initiated to evaluate the clinical potential of this combination. Beyond oncology, we have taken this approach in the past with KPT-350, an oral SINE compound for which we developed a preclinical data package supporting potential efficacy in a number of neuro-inflammatory conditions, which Biogen acquired from us in early 2018. KPT-350 was renamed BIIB100 and is currently in clinical evaluation to treat ALS. We believe that investing in the recruitment of exceptional advisors, employees, and management is critical to our continued leadership in the nuclear transport field. We are collaborating with leading patient advocacy groups to provide education on the science behind our SINE compounds and to support the development and execution of clinical trials. We have advanced the understanding and potential application of SINE compounds in cancer treatment through a broad range of collaborations with leading institutions engaged in evaluating SINE compounds in clinical trials in the United States, Canada, many European countries, Australia, India, Israel, Singapore and elsewhere.
- **Continue Developing our Pipeline of Novel Drug Candidates.** To date, we have identified several drug candidates: our oral SINE compounds selinexor, eltanexor and verdinexor and our oral dual

PAK4/NAMPT inhibitor, KPT-9274. A fifth program, KPT-350 for ALS and other neuro-inflammatory conditions, was sold to Biogen in January 2018. We may also identify or in-license novel drug candidates for development in oncology in the future.

- **Maximize the Value of Our Other 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 other SINE compounds in non-oncology indications. For example, in May 2018, we licensed the development and commercial rights to Antengene for verdinexor in the non-oncology field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam. As described above, in January 2018, we entered into an asset purchase agreement with Biogen pursuant to which Biogen acquired KPT-350 as well as certain related assets with an initial focus in ALS.

Our Focus: Nuclear Transport

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 accumulation of DNA damage (mutations, chromosomal translocations and other abnormalities) by monitoring DNA for damage, and if damage is detected, the tumor suppressor proteins direct the cell to attempt to repair it. However, if the DNA damage is too severe, the tumor suppressor proteins direct the cell to die in a process called apoptosis.

Proteins, however, are not made inside the nucleus but rather 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 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.

Eight exportins have been identified in human cells. One such export carrier protein was discovered in 1999 and is called exportin 1, or XPO1 or CRM1. XPO1 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, or eIF4E, 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. eIF4E 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 I κ B, which inhibits a protein called NF- κ B. NF- κ B 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. By exporting I κ B out of the nucleus, XPO1 augments NF- κ B activity.

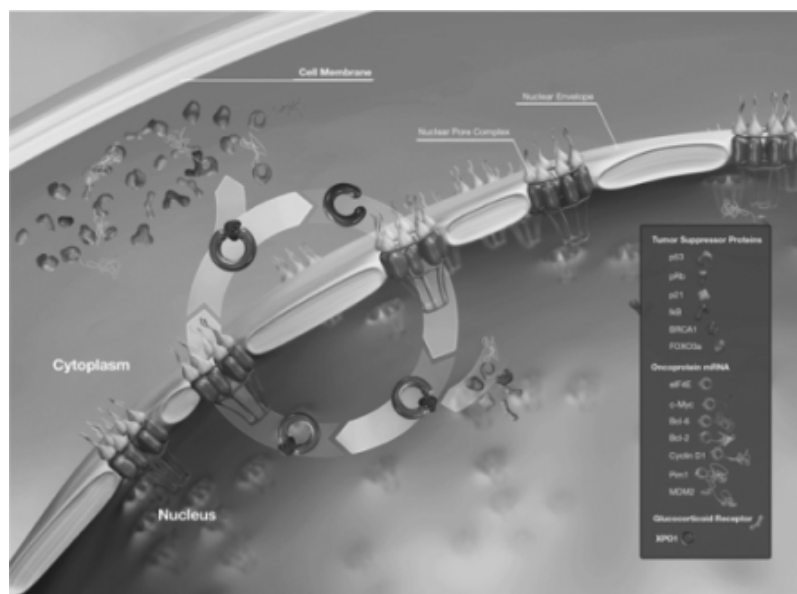
XPO1 levels are reported to be elevated in nearly all cancer cells when compared to their healthy cell counterparts. Therefore, these elevated levels of XPO1 in cancer cells mediate the rapid export of tumor

suppressor proteins as well as I κ B and eIF4E out of the nucleus. When compared to healthy cells, the increased export of tumor suppressor proteins in cancer cells may lead to reduced monitoring for DNA damage, the normal triggering of apoptosis and increased NF- κ B activity. Higher levels of XPO1 expression in cancer cells is also generally correlated with resistance to chemotherapy and poor prognosis of patients.

Inhibiting XPO1 leads to accumulation of tumor suppressor proteins as well as eIF4E and I κ B in the cell nucleus, which has been confirmed in a variety of preclinical models as well as in tumor biopsy tissues from patients treated with selinexor. Nuclear retention of tumor suppressor proteins increases their efficiency in detecting DNA damage and subsequently triggering apoptosis in cancer cells. In addition, blocking XPO1 can cause accumulation of eIF4E-bound growth-promoting mRNAs, which may cause a reduction in the levels of growth-promoting proteins in cancer cells; this has also been confirmed in preclinical models and in patients' tumor biopsy tissues. Accumulation of I κ B in the nucleus inhibits NF- κ B, which may be beneficial in overcoming chemotherapy resistance and in treating autoimmune, inflammatory, and neuro-inflammatory disease; this too has been detected in both preclinical models and in human cancer tissues from treated patients. For these reasons, we believe blocking XPO1 is a good strategy for treating cancer as well as autoimmune, inflammatory and neuro-inflammatory diseases. The figure below depicts the process by which XPO1 mediates the nuclear transport process.

XPO1 Mediation of Nuclear Transport

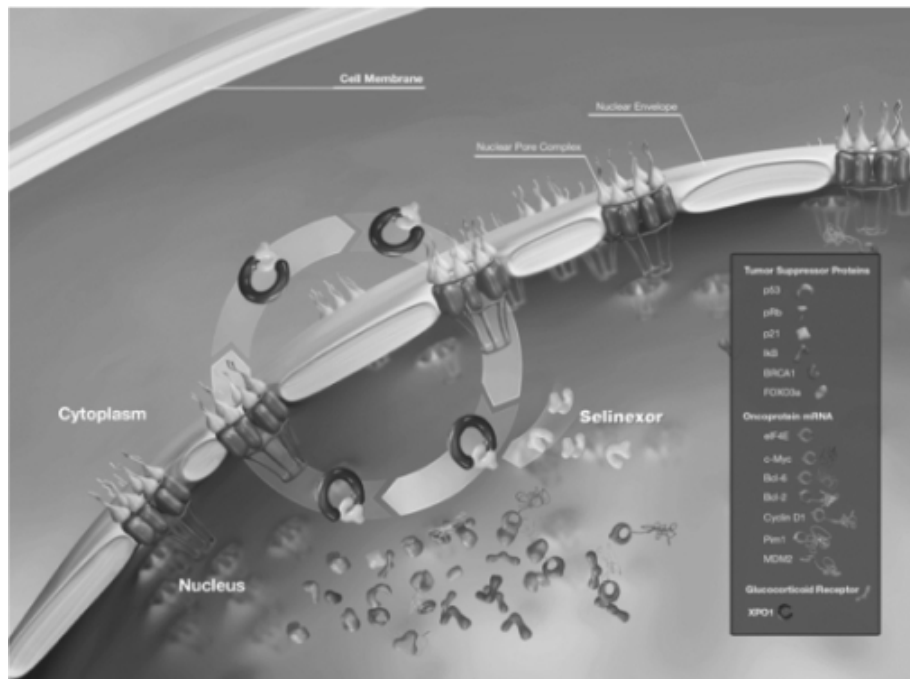
Our Approach: Targeting Nuclear Export with SINE Compounds



XPOVIO, our approved XPO1 inhibitor, and our drug candidates are first-in-class, oral, SINE compounds. SINE compounds inhibit XPO1-mediated nuclear export by strongly, yet reversibly, binding to the XPO1 cargo binding site, effectively blocking the XPO1-cargo protein interaction. The transient XPO1 inhibition period that we have observed to date with our SINE compounds appears to be sufficient for elevation of tumor suppressor protein levels and I κ B in the nucleus. 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. Healthy cells also accumulate tumor suppressor proteins in the presence of a

SINE compound, but they do not undergo apoptosis after transient XPO1 inhibition because they have minimal or no DNA damage. The figure below depicts the process by which SINE compounds inhibit the XPO1-mediated nuclear export of tumor suppressor proteins.

Transient XPO1 Inhibition by SINE Compounds



In addition to cancer, our SINE compounds have demonstrated the potential to provide therapeutic benefit in a number of other indications. Specifically, SINE compounds have shown evidence of activity in preclinical models of viral infections, neurological disorders, inflammation and autoimmune diseases.

Our Initial Indication: Cancer

According to the World Health Organization, cancer is the second leading cause of death globally and responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer. Additionally, cancer is one of the most important health issues facing patients in the United States. The American Cancer Society estimates that in the United States, more than 16.9 million Americans with a history of cancer were alive on January 1, 2019 and more than 1.8 million new cancer cases are expected to be diagnosed in 2020. Approximately 600,000 Americans are expected to die of cancer in 2020.

The most common methods for treating patients with cancer are a combination of surgery, radiation, and drug therapy. Locoregional therapies, such as surgery and radiation therapy, are particularly effective with localized disease. However, in situations where the cancer has spread beyond the primary site or cannot otherwise be treated through locoregional therapies, physicians generally use systemic drug therapies. In many cases, drug therapy includes combinations of several different drugs. An early approach to cancer treatment was through cytotoxic drugs that kill rapidly proliferating cancer cells by nonspecific mechanisms, such as disrupting cell metabolism or causing damage to cellular components required for survival and rapid growth. While these

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drugs have been effective in the treatment of some cancers, they act in an indiscriminate manner, killing healthy cells as well as cancer cells. Due to their mechanism of action, many cytotoxic drugs have a narrow dose range above which the toxicity causes unacceptable or even fatal levels of damage and below which the drugs are not effective in promoting cancer cell death. A different approach to pharmacological cancer treatment has been to develop drugs referred to as targeted therapeutics, which target specific biological molecules in the human body that play a role in the rapid cell growth and spread of cancer. Targeted therapeutics are designed specifically to exploit vulnerabilities in cancer cells to improve efficacy and to minimize side effects. The drugs are designed to either attack a target that causes uncontrolled growth of cancer cells because of a genetic alteration more often found in cancer cells than in healthy cells or attack a target that cancer cells are more dependent on for their growth than are healthy cells.

Our SINE compounds are novel therapies specifically designed to force nuclear accumulation in the levels of multiple tumor suppressor and growth regulatory proteins. When tumor suppressor proteins are located in the cell nucleus, they assess the integrity of a cell's DNA. In cells with heavily damaged DNA, such as cancer cells, these tumor suppressor proteins induce cell death, or apoptosis. 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 have the potential to provide therapeutic benefits across a broad range of both hematological and solid tumor malignancies and benefit a wider range of patients. Additionally, and as supported by its mechanism of action and preclinical and clinical data, we believe that selinexor has the potential for additive or synergistic benefit with approved and experimental therapies in treating cancer patients. As a result, we believe that selinexor has the potential to serve as a backbone therapy across multiple hematological and solid tumor malignancies as part of a variety of combination therapies.

Since our founding by Dr. Sharon Shacham in 2008, our goal has been to establish a leading, independent oncology business. We are led by Dr. Shacham, our President and Chief Scientific Officer, and Dr. Michael Kauffman, our Chief Executive Officer. Dr. Kauffman played a leadership role in the development and approval of Velcade at Millennium Pharmaceuticals and of Kyprolis while serving as Chief Medical Officer at Proteolix and then Onyx Pharmaceuticals. Both prior to her founding of Karyopharm and while at Karyopharm, Dr. Shacham has played a leadership role in the discovery and development of many novel drug candidates, which have been or are being tested in human clinical trials.

Since our inception, we have devoted most of our efforts to research and development. Beginning in July 2019, we have generated revenue from the commercial sale of XPOVIO[®] (selinexor). Net product sales for the year ended December 31, 2019 was \$30.5 million. As of December 31, 2019, we had an accumulated deficit of \$873.3 million. We had net losses of \$199.6 million, \$178.4 million and \$129.0 million for the years ended December 31, 2019, 2018 and 2017, respectively.

Our Strategic Relationships

On May 23, 2018, we entered into a license agreement with Antengene Therapeutics Limited, a corporation organized and existing under the laws of Hong Kong, or 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 granted Antengene exclusive rights to develop and commercialize, at its own cost, 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. We licensed the development and commercial rights to Antengene for selinexor and eltanexor in the oncology field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the oncology field, as well as verdinexor in the non-oncology field in mainland China, Taiwan, Hong Kong, Macau, South Korea, and the ASEAN countries (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam). Under the terms of the Antengene Agreement, we received an upfront cash payment of \$11.7 million and are entitled to receive up to \$105.0 million in milestone payments

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from Antengene if certain development goals are achieved and up to \$45.0 million in milestone payments from Antengene if certain sales milestones are achieved. We are further eligible to receive tiered double-digit royalties based on future net sales of selinexor and eltanexor in China and Macau, and tiered single- to double-digit royalties based on future net sales of KPT-9274 and verdinexor in the licensed territories. Antengene's obligations under the license agreement have been guaranteed by Antengene Corporation Co. Ltd.

According to publicly available information, Antengene filed Clinical Trial Applications, or CTAs, in China with the National Medical Products Administration, or NMPA, for selinexor in multiple myeloma and DLBCL in 2019. The multiple myeloma CTA, known as MARCH, supports a clinical study of selinexor plus dexamethasone in patients whose disease is refractory to lenalidomide and bortezomib. The first patient in this study was enrolled in September 2019. The DLBCL CTA, known as SEARCH, supports a clinical study of selinexor both as single agent and in combination with ATG-008, for the treatment of relapsed/refractory DLBCL. Also, Antengene announced on January 3, 2020 that the Food and Drug Administration, Ministry of Health and Welfare, Taiwan has recently approved the commencement of a phase I open-label clinical trial for the PAK4/NAMPT dual target oral inhibitor KPT-9274 in patients with advanced solid tumors or NHL which have progressed despite standard therapy, for whom no standard therapy exists, or who have refused standard therapy.

On January 24, 2018, we entered into an asset purchase agreement with Biogen pursuant to which Biogen acquired our oral SINE compound KPT-350 and certain related assets. XPO1 mediates the nuclear export of multiple proteins that impact neurological and inflammatory processes. Consequently, inhibition of XPO1 by KPT-350 results in a reduction in inflammation and an increase in anti-inflammatory and neuroprotective responses. KPT-350 penetrates the blood brain barrier to a greater degree than other SINE compounds. Preclinical data generated largely by external collaborators show efficacy of KPT-350 and related SINE compounds in animal models of amyotrophic lateral sclerosis, multiple sclerosis, traumatic brain injury, epilepsy, and other neuro-inflammatory indications. We received a one-time upfront payment of \$10.0 million from Biogen and are eligible to receive additional payments of up to \$207 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 country-by-country basis. According to publicly available information, an IND application for KPT-350 was filed in December 2018 and the first patient was dosed in a Phase 1 study of sporadic ALS in June 2019.

Effective October 11, 2017, we entered into an exclusive license agreement with Ono Pharmaceutical Co., Ltd., or Ono, whereby Ono received rights to develop and commercialize selinexor and eltanexor at its own cost and expense, for the diagnosis, treatment and/or prevention of all human oncology indications in Japan, South Korea, Taiwan, Hong Kong, and the ASEAN countries, which we refer to as the Ono Territory. In exchange, we received a one-time upfront payment of ¥2.5 billion (approximately US\$21.9 million) from Ono and retain all rights to selinexor and eltanexor outside the Ono Territory. We are eligible to receive up to an additional ¥19.15 billion (approximately US\$176.2 million at the exchange rate on December 31, 2019) if specified future development and commercial milestones are achieved by Ono. We are also eligible to receive low double-digit royalties based on future net sales of selinexor and eltanexor in the Ono Territory. Ono will have the ability to participate in any global clinical study of selinexor and eltanexor and will bear the cost and expense for patients enrolled in clinical studies in the Ono Territory.

In May 2017, we entered into an exclusive licensing agreement with Anivive Life Sciences, Inc., or Anivive, pursuant to which Anivive received worldwide rights to research, develop and commercialize verdinexor for the treatment of cancer in companion animals. In exchange, we received an upfront payment of \$1.0 million and a subsequent milestone of \$250,000 and are eligible to receive up to \$43.25 million in future regulatory, clinical and commercial milestone payments, assuming approval in both the United States and the European Union. In addition, Anivive agreed to pay us up to low double-digit royalty payments based on future

net sales of verdinexor. If approved, we believe that verdinexor would represent the first non-chemotherapy-based approval for the treatment of dog lymphoma.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our drug 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 United States and in foreign jurisdictions related to our proprietary technology and drug 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 drug candidates. As of February 10, 2020, we were the sole owner of 20 patents in the United States and we had 10 pending patent applications in the United States, two pending international applications filed under the Patent Cooperation Treaty, or PCT, 59 granted patents and 96 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 drug candidates as of February 10, 2020 are summarized below.

- **Selinexor (KPT-330):** Our selinexor patent portfolio covers the composition of matter and methods of use of selinexor, as well as methods of making selinexor, and consists of five issued U.S. patents (two patents are specific to selinexor, two other patents cover both selinexor and verdinexor and the fifth patent covers polymorphs of selinexor), 23 issued foreign patents, 43 pending foreign patent applications, two pending U.S. non-provisional applications, including one directed to polymorphs of selinexor and one pending U.S. provisional patent application. Any patents that may issue in the United States as part of our selinexor patent portfolio, with the exception of a patent directed to the polymorphs of selinexor, will expire in 2032, absent any terminal disclaimer, patent term adjustment due to administrative delays by the United States Patent and Trademark Office, or 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 United States 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 patent issued in foreign jurisdictions will likewise expire in 2035. If a non-provisional patent application claiming the benefit of the pending U.S. provisional patent application referenced above is filed in 2020, any patents that may issue from such applications will expire no earlier than 2040.
- **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, 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, nine issued foreign patents, 20 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 United States 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 United States 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 nine issued U.S. patents, five issued foreign patents, two pending U.S. non-provisional patent applications, and 28 pending foreign patent applications in total. Any patents that may issue in the United States based on the pending U.S. non-provisional applications will expire in 2034 for the earliest filed application and 2036 for the remaining application, 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 or 2036. Foreign patent applications covering the composition of matter and methods of use of KPT-9274 have been filed in 21 countries/regions.

In addition to the patent portfolios covering our key drug candidates, as of February 10, 2020, our patent portfolio also includes five patents (U.S. Patent Nos. 8,513,230, 9,303,000, 9,428,490, 9,550,757 and 10,526,295) 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 and biomarkers for XPO1 inhibitors. In the United States, 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 drug names (examination is currently suspended), and KARYFORWARD and a KARYFORWARD logo for our financial aid and charitable services. Outside the United States, XPOVIO is registered or pending in thirty additional jurisdictions, and is registered or pending in Katakana in Japan, Hangul in South Korea, and Chinese characters in Taiwan. We also have registrations or applications for eight additional possible drug 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 United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, 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 drug 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 drug 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.

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As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our drug 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 drug candidate we may develop, it is possible that, before any of our drug 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 competitive advantages, we face potential 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 drug candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

There are several 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, only one other company with an XPO1 inhibitor has enrolled patients in clinical trials at the present time. Stemline Therapeutics, Inc. announced in January 2015 that it had exclusively licensed the rights to develop and commercialize SL-801 (felezonexor), an oral XPO1 inhibitor, from CanBas Co., Ltd. In December 2015, Stemline announced the opening of its IND and planned initiation of a clinical development program in multiple cancer types. Stemline currently has a Phase 1 trial that is open and enrolling patients with advanced solid tumors. Updates were provided at the ESMO 2019 annual meeting indicating one patient had realized a partial response and some other patients had experienced stable disease.

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 and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even

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

The key competitive factors affecting the success of any approved oncology drug product, including our drug candidates, if approved, are likely to be their efficacy, safety, 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 drugs, or commercialize existing drugs in new indications, and those drugs are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any drugs that we may develop. Our competitors also may obtain FDA or other regulatory approval for their drugs 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 drugs are expected to become available on a generic basis over the coming years. As we have seen with XPOVIO, and in multiple myeloma, if we obtain marketing approval for our other drug candidates or for selinexor 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 drug 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 drug 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 drugs 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 drugs in late stage clinical development to treat cancer and the other indications on which we plan to initially focus. These drugs in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our drug candidates for which we obtain marketing approval.

XPOVIO and, if approved, our other lead drug candidates may compete with the investigational therapies and currently marketed drugs discussed below.

Multiple Myeloma

Over the past 15 years, ten agents have been approved in the United States for the treatment of patients with multiple myeloma: bortezomib (Velcade[®], Takeda), lenalidomide (Revlimid[®], Celgene), thalidomide (Thalomid[®], Celgene), liposomal doxorubicin (Doxil[®], Janssen), carfilzomib (Kyprolis[®], Amgen), pomalidomide (Pomalyst[®], Celgene), panobinostat (Farydak[®], Novartis), daratumumab (Darzalex[®], Janssen), elotuzumab (Empliciti[®], BMS), and ixazomib (Ninlaro[®], Takeda). Approved indications range from the treatment of newly diagnosed patients to those with relapsed and/or refractory multiple myeloma.

Several other anti-cancer agents are in late-stage development for the treatment of patients with multiple myeloma, including anti-B cell maturation antigen (BCMA), based CAR-T therapies such as bb2121 and CC-93269 (Bluebird Bio/Celgene/BMS), JCHARHI25 (Juno Therapeutics/Celgene), P-BCMA-101 (Johnson &

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Johnson/Poseida Therapeutics), JNJ-4528 (LCAR-B38M, Johnson & Johnson/Legend BioTech) and CAR-T-BCMA (Novartis); monoclonal antibodies such as isatuximab (Sanofi), TAK-079 (Takeda); antibody-drug conjugates such as belantamab mafodotin (GSK2857916, GlaxoSmithKline); bi-specific antibodies such as AMG420 (Amgen), REGN5458 (Regeneron) and PF-06863135 (Pfizer); and other novel agents such as ibrutinib (Imbruvica[®], Abbvie/Roche), venetoclax (Venclexta[®], Abbvie), plitidepsin (PharMar), masitinib (AB Sciences), filanesib (Array Biopharma), oprozomib (Amgen), ricolinostat (Celgene) and melflufen (Oncopeptides).

Non-Hodgkin's Lymphoma (NHL)

The initial therapy for DLBCL typically consists of multi-agent cytotoxic drugs in combination with the monoclonal antibody rituximab (Rituxan[®], Roche). In patients with DLBCL who are not elderly and who have good organ function, high dose chemotherapy with stem cell transplantation is often used. Over the past two years, three therapeutic interventions have been approved in the United States for the treatment of patients with relapsed refractory DLBCL, or RR DLBCL, who have received at least two prior therapies: tisagenlecleucel (Kymriah[®], Novartis) and axicabtagene ciloleucel (Yescarta[®], Kite/Gilead), both CAR-T therapies, and polatuzumab vedotin (Polivy[®], Genentech/Roche). On December 30, 2019, MorphoSys announced its submission of a biologics license application (BLA) to the FDA for tafasitamab in RR DLBCL. Newer targeted agents such as the BTK inhibitor ibrutinib (Imbruvica[®], Pharmacyclics) and the immunomodulatory drug lenalidomide (Revlimid[®], Celgene) have also shown activity in DLBCL. There are also a number of other widely used anti-cancer agents that have broad labels which include NHL, and some of these are being evaluated alone or in combination for the treatment of patients with DLBCL that have relapsed after treatment with chemotherapy. Other anti-cancer agents are also being evaluated in the treatment of DLBCL, including but not limited to, tafasitamab (MOR-208, MorphoSys), polatuzumab vedotin (Polivy[™], Roche), magrolimab (Hu5F9-G4, Forty Seven, Inc.), umbralisib/ublituximab (TG Therapeutics), mosunetuzumab (Roche), ADCT-402 (ADC Therapeutics), zanubrutinib (Brukinsa[™], Beigene), everolimus (Afinitor[®], Novartis), venetoclax (Venclexta[®], Abbvie), acalabrutinib (Calquence[®], Acerta Pharma), blinatumomab (Blincyto[®], Amgen), durvalumab (Imfinzi[®], AstraZeneca), nivolumab (Opdivo[®], BMS), pembrolizumab (Keytruda[®], Merck), avelumab (Bavencio[®], Pfizer/EMD Serono) and brentuximab vedotin (Adcetris[®], Seattle Genetics). In addition, other CAR-T therapies are currently in clinical development.

Dedifferentiated Liposarcoma (DDLs)

Sarcomas are a group of cancers which arise from connective tissue and bone, of which more than 50 subtypes exist. Liposarcoma is one of the more common types of soft tissue sarcoma. The initial treatment for liposarcoma is surgery with or without radiotherapy when possible. When liposarcoma is not amenable to surgery (i.e., unresectable), various systemic treatments, including multiagent and sometimes single agent chemotherapy are used. Agents used in combination therapies include: doxorubicin, ifosfamide, epirubicin, gemcitabine, dacarbazine, docetaxel and vinorelbine. There are a number of anti-cancer agents that have board soft tissue sarcoma labels and are typically used as single agents after initial systemic therapy, which include liposomal doxorubicin, temozolomide, vinorelbine, pazopanib (Votrient[®] Novartis), larotrectinib (for neurotrophic tyrosine receptor kinase, or NTRK, gene fusion-positive sarcomas—Vitrakvi[®], Bayer) and entrectinib (for NTRK gene fusion-positive sarcomas—Rozlytrek[®], Genentech/Roche).

Selinexor is being evaluated in patients with advanced, unresectable, dedifferentiated relapsed or refractory liposarcoma who have received at least two prior therapies. Two agents have been approved in the United States for the management of unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen: eribulin (Halaven[®], Eisai Inc. 2017) and trabectedin (Yondelis[®], Janssen 2019). Other anti-cancer agents are also being evaluated in the treatment of dedifferentiated liposarcoma, including but not limited to HDM201 and LEE011 (Novartis), cabazitaxel (Jevtana[®], Sanofi), abemaciclib (Verzenio[®], Lilly), plitidepsin (PharmaMar), Ipilimumab/Nivolumab (BMS), and Pembrolizumab (Keytruda[®], Merck). The effectiveness of existing treatments for unresectable or metastatic liposarcoma remains limited and few trials have specifically evaluated dedifferentiated liposarcoma at an advanced stage.

Competition with XPO1 Inhibitors

Drug compounds currently in preclinical studies, if developed and approved, could also be competitive with our drug candidates, if approved. In January 2015, Stemline Therapeutics, Inc. announced that it had exclusively licensed the rights to develop and commercialize SL-801, an XPO1 inhibitor, from CanBas Co., Ltd. Stemline currently has a Phase 1 trial that is open and enrolling patients with advanced solid tumors and updates were provided at the 2019 ESMO annual meeting indicating one patient had realized a partial response and some other patients had experienced stable disease. Additionally, Kosan Biosciences Inc. (acquired by Bristol-Myers Squibb Company) had evaluated compounds derived from leptomycin B in preclinical studies. To our knowledge, the Kosan compounds are not currently being developed and have never entered human studies.

With respect to indications other than cancer, there are many currently marketed therapies and drugs in late-stage clinical development to treat non-oncology indications which we may develop of our XPO1 inhibitors. However, to our knowledge, there are no other XPO1 inhibitors in clinical development for the treatment of any diseases other than cancer, including indications such as autoimmune and inflammatory diseases or wound healing. There is no published information on the use of the preclinical compounds that have been developed by Kosan Biosciences or CanBas Co./Stemline in models other than cancer.

Competition with PAK4/NAMPT Dual Inhibitors

Our first-in-class PAK4/NAMPT dual inhibitor KPT-9274, if developed and approved, would compete with currently marketed therapies and drugs in clinical development to treat cancer. However, there are currently no marketed therapies that target PAK4 and/or NAMPT. We are not aware of any company focusing on the development of a PAK4/NAMPT dual inhibitor. KPT-9274 is orally bioavailable and has demonstrated in pre-clinical studies consistent pharmacokinetics properties, minimal brain penetration, and minimal inhibition of cytochrome P450 (CYP-450) enzymes. In early animal models, KPT-9274 has not shown the retinal and cardiac effects observed with certain NAMPT inhibitors.

Pfizer Inc. developed PF-03758309, a non-selective PAK inhibitor, meaning that this compound inhibited several of the PAK family members, and not solely PAK4, through Phase 1 clinical development, but that compound had poor oral bioavailability in both animals and humans and, to our knowledge, development has been discontinued. We are aware that PAK4 biology is being evaluated preclinically by AstraZeneca plc and Genentech, Inc. (acquired by Roche Holding AG). We are aware of a possible first in human clinical trial by Arcus Bioscience for its PAK inhibitor in 2020. We are not aware of any other PAK4 inhibitors that are in clinical development at the present time.

In addition to KPT-9274, we are aware of three NAMPT inhibitors that have entered phase 1/2 human clinical trials in patients with solid tumors or lymphomas. These compounds include GMX1778 (also known as CHS-828, Teva), GMX1777 (water-soluble derivative of GMX1778, Teva), and APO866 (also known as FK866 and WK175). APO866 and GMX1777 was delivered as parenteral infusions, while GMX1778 was evaluated by oral dosing. The safety and preliminary efficacy of these inhibitors as reported in the literature appeared to show unfavorable pharmacokinetics properties (limited/no oral bioavailability, poor plasma stability, high inter- and intra-patient variability, and drug-drug interactions). To our knowledge, development of these inhibitors were discontinued. We are also aware that OT-82 (OncoTartis) has advanced to first in human clinical development stage. We are aware that NAMPT biology is being evaluated by Genentech, Inc., Eli Lilly & Company, Millennium/Takeda Pharmaceutical Company Ltd., OncoTartis, Inc., Arcus Bioscience, Aurigene Discovery Technologies Limited, and at some academic institutions. We are not aware of any other NAMPT inhibitors in clinical development.

Manufacturing

We do not have any manufacturing facilities or personnel. We currently utilize and expect to continue to utilize third parties for the manufacture and testing of our preclinical, clinical, and commercial drug products. We

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have engaged one third-party manufacturer to obtain the active pharmaceutical ingredient for selinexor for clinical and commercial testing. We have engaged a separate third-party manufacturer for fill-and-finish (tableting) services and have entered into a three-year supply agreement for the manufacture of selinexor 20 mg tablets with this manufacturer. We obtain all other selinexor supplies or materials on a purchase order basis and do not have a long-term supply arrangement in place at this time. We currently maintain sufficient inventories to exceed our two-year forecasts for selinexor and do not have arrangements in place for a redundant supply. For all of our drug candidates, we intend to identify and qualify additional manufacturers to provide the active pharmaceutical ingredient and fill-and-finish services as part of our long-term commercial supply plans.

All of our drug products/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 has been developed to meet our large-scale manufacturing needs and do not require unusual equipment in the manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, or 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 United States 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 United States

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act, or 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 United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or 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, or 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, or 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;

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- 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, or 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, or 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 adverse events 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.

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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 FDA certain 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 investigational new drug 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 an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee or DSMB. 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, or NIH, for public dissemination on its ClinicalTrials.gov website. Similar requirements for posting clinical trial information are present in the European Union (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 investigational new drug 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 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 investigational new drug 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.

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Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events 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. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, 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 drug has been associated with unexpected serious harm to patients. 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 drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

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 2020 is \$2,942,965 for an application requiring clinical data. The sponsor of an approved NDA is also subject to a program fee for fiscal year 2020 of \$325,424. 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 adverse events, 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, or 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

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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 21st Century Cures Act, or 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, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. 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 adverse events 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;

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- 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 United States, 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, or PDMA, and its implementation regulations, as well as the Drug Supply Chain Security Act, or 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, or 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, or 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, or 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 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 a new chemical entity, 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, or 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 United States 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 United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States 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 be receiving 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

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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 U.S. Patent and Trademark Office 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 United States

In addition to pursuing approval of our drug candidates for use in human beings, we may also seek approval of certain drug candidates for veterinary applications. As with new drug products for human beings, new animal drugs may not be marketed in the United States 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 or CVM at FDA is responsible for determining whether a new veterinary product should be approved on the basis of a 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, or 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 or 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 United States, 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 in the European Union

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 a 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 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 a marketing authorization application, or MAA, either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the European Commission 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.

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Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the European Medicines Agency, or 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 European Commission, whose decision is binding on all member states.

Within this framework, manufacturers may seek approval of hybrid medicinal products under Article 10(3) of Directive 2001/83/EC. Hybrid applications rely, in part, on information and data from a reference product and new data from appropriate pre-clinical 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 in the European Union

Requirements for the conduct of clinical trials in the EU including Good Clinical Practice, or 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 CTA is submitted, which must be supported by an investigational medicinal product dossier, or 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.

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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. As of January 1, 2020, the website of the European Commission 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 European Commission publishes a notice of this confirmation. The website indicated that the audit was expected to commence in December 2020.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trial 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.

PRIME Designation in the EU

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, or 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, or 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 marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated Agency contact and rapporteur from the CHMP or Committee for Advanced Therapies, or CAT, 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 in respect of 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 European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. Any authorization which is not followed by

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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 European Union

In the EU, new chemical entities 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 authorization 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 United States, 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, or 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, or 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 United States, 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. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom, or 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. Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Discussions between the UK and the UK have so far mainly focused on finalizing withdrawal issues and transition agreements but have been extremely difficult to date. To date, only an outline of a trade agreement has been reached. Much remains open but the Prime Minister has indicated that the UK will not seek to extend the transitional period beyond the end of 2020. If no trade agreement has been reached before the end of the transitional period, there may be significant market and economic disruption. The Prime Minister has also indicated that the UK will not accept high regulatory alignment with the EU.

Since the regulatory framework for pharmaceutical products in the UK 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 UK. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom.

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 United States 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. 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

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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 United States, 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, or 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 United States, 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.

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug 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 drug candidate to currently available therapies. For example, the EU provides options for its member states to restrict the range of drug 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 drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

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, or HIPAA, 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, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

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- 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 the Centers for Medicare & Medicaid Services, or 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 United States 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 United States.

By way of example, the United States 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, or 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 potential drug 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," or AMP, 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 new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

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- the Independent Payment Advisory Board, or 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 United States 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. 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, will become 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 inseparable 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. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The Trump Administration recently represented to the Court of Appeals considering this judgment that it does not oppose the lower court's ruling. On July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. On December 18, 2019, that 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. On January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any

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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. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. This decision is under review by the U.S. Supreme Court during its current term. The full effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

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, 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. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

For example, on May 11, 2018, the Trump Administration issued a plan to lower drug prices. Under this blueprint for action, the Trump Administration indicated that the Department of Health and Human Services, or HHS, will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. In addition, on December 23, 2019, the Trump Administration published a proposed rulemaking that, if finalized, would allow states or certain other non-federal government entities to submit importation program proposals to 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. 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).

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 product candidates or additional pricing pressures.

Employees

As of February 14, 2020, we had 347 full-time employees. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that relations with our employees are good.

Information about our Executive Officers

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

<u>Name</u>	<u>Age</u>	<u>Position</u>
Michael G. Kauffman, M.D., Ph.D.	56	Chief Executive Officer and Director
Sharon Shacham, Ph.D., M.B.A.	49	President and Chief Scientific Officer
Christopher B. Primiano, J.D., M.B.A.	39	Executive Vice President, Chief Business Officer, General Counsel and Secretary
Ran Frenkel, RPh.	51	Chief Development Operations Officer
Jatin Shah, M.D..	45	Executive Vice President, Chief Medical Officer
Tanya Lewis, M.S.	49	Executive Vice President, Chief Regulatory Officer and Quality Officer
Michael Mason	45	Senior Vice President, Chief Financial Officer and Treasurer

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 January 2011 to December 2013 and as Chief Medical Officer from December 2012 to December 2013. Prior to joining Karyopharm, he was Chief Medical Officer of Onyx Pharmaceuticals Inc., a biopharmaceutical company, from November 2009 to December 2010. From November 2008 to November 2009, Dr. Kauffman was Chief Medical Officer of Proteolix Inc., which was acquired by Onyx Pharmaceuticals. At Proteolix, he led the development of Kyprolis[®] (carfilzomib), a novel proteasome inhibitor approved in refractory myeloma by the Food and Drug Administration in July 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., a 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., a private biopharmaceutical company focused on G protein-coupled receptors (GPCR), from 2002 until its merger into Epix Pharmaceuticals in 2006. In that role, he led the merger of Predix Pharmaceuticals and Epix Pharmaceuticals, oversaw the discovery and development of four new clinical candidates and led collaboration transactions with Amgen and GlaxoSmithKline. From March 2000 to September 2002, Dr. Kauffman was Vice President, Clinical at Millennium Pharmaceuticals, Inc., a biopharmaceutical company, where he led the Velcade[®] development program. From September 1997 to March 2000, Dr. Kauffman held a number of senior positions at Millennium Predictive Medicine, Inc., a biopharmaceutical company and a subsidiary of Millennium Pharmaceuticals, 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 August 1995 to September 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 currently serves on the board of directors, nominating and governance committee and research and development committee of Infinity Pharmaceuticals, Inc., a public biopharmaceutical company, on the board of directors and audit committee and as chairman of the compensation committee of Kezar Life Sciences, Inc., also a public biopharmaceutical company, and is the lead director and serves on the board of directors and compensation committee of Verastem Inc., also a public biopharmaceutical company. Dr. Kauffman previously served on the board of directors and compensation and audit committees of Zalicus Inc., a biotechnology company. Dr. Kauffman received his B.A. in Biochemistry

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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 and has served as our President since December 2013, and as our Chief Scientific Officer since October 2010. Dr. Shacham served as our President of Research and Development from December 2012 to December 2013, as our Head of Research and Development from October 2010 to December 2012 and as our President and Chief Executive Officer from October 2010 to January 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 drug candidate. Dr. Shacham co-chairs our Scientific Advisory Board. Prior to founding Karyopharm, from 2006 to April 2009, she was Senior Vice President of Drug Development at Epix Pharmaceuticals, Inc., 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 Pharmaceuticals Inc. from July 2000 until Predix's merger into Epix Pharmaceuticals 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.

Christopher B. Primiano, J.D., M.B.A. Mr. Primiano joined Karyopharm in March 2014 as Vice President, Corporate Development, General Counsel and Secretary, and was appointed Senior Vice President, Corporate Development, General Counsel and Secretary in September 2015; Senior Vice President, Operations, Business Development, General Counsel and Secretary in November 2016 and Executive Vice President, Chief Business Officer, General Counsel and Secretary in January 2018. Prior to joining Karyopharm, Mr. Primiano was a Counsel at Wilmer Cutler Pickering Hale and Dorr LLP, where he had practiced law since October 2012. From August 2010 to August 2012, he served as Vice President, Corporate Development, General Counsel and Secretary of GlassHouse Technologies, Inc., an information technology consulting company, where he led global legal operations and managed asset and subsidiary acquisition and sale activity. Mr. Primiano began his career at Gunderson Dettmer Stough Villeneuve Franklin & Hachigian LLP, where he practiced law from August 2006 to July 2010. Mr. Primiano received a B.A. in Political Economy and English from Georgetown University, an M.B.A. from the Boston College Carroll School of Management and a J.D. from Boston College Law School.

Ran Frenkel, RPh. Mr. Frenkel was appointed Executive Vice President, Worldwide Development Operations of Karyopharm in October 2014 and was appointed Chief Development Operations Officer in January 2015. Prior to joining Karyopharm, Mr. Frenkel held a number of senior management roles in Europe, Israel and the United States, most recently as Managing Director EMEA from January 2013 to October 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 VP International Business Development at Clinipace Worldwide from July 2011 to January 2013. Prior to joining Clinipace Worldwide, from January 2007 to August 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.

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 September 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

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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.

Tanya Lewis, M.S. Ms. Lewis joined Karyopharm in October 2018 as Senior Vice President, Regulatory and Quality Affairs and was appointed Executive Vice President, Chief Regulatory Officer and Quality Officer in November 2019. 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 ZEZULA[®]. Most recently Ms. Lewis served as Vice President, Regulatory and Quality Affairs for Syros Pharmaceuticals, a pharmaceutical company, from January 2017 to July 2018. Prior to joining Syros Pharmaceuticals, Inc., Ms. Lewis served as Vice President, Regulatory Affairs and Quality Assurance for Idera Pharmaceuticals, Inc., a pharmaceutical company, from October 2015 to December 2016. Prior to joining Idera Pharmaceuticals, Ms. Lewis served as Vice President, Regulatory Affairs for Tesaro, Inc., a pharmaceutical company, from October 2011 to June 2015. 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 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 February 2011 until February 2019, as its Principal Accounting Officer from February 2011 to October 2018, and as its Principal Financial Officer from February 2011 to June 2016 and from January 2017 to May 2017. From December 2005 to February 2011, Mr. Mason served as Alnylam's Corporate Controller. From May 2000 through November 2005, Mr. Mason served in several finance and commercial roles at Praecis Pharmaceuticals Incorporated, 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.

Our Corporate Information

Karyopharm was incorporated under the laws of the state of Delaware on December 22, 2008 under the name Karyopharm Therapeutics Inc. Our principal executive offices are located at 85 Wells Avenue, 2nd Floor, Newton, Massachusetts 02459. Our telephone number is (617) 658-0600, and our website is located at www.karyopharm.com. 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.

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, or the Exchange Act. 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, or SEC. 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.

Our Code of Business Conduct and Ethics, Corporate Governance Guidelines and the charters of the Audit, Compensation, Nominating and Corporate Governance and 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. RISK FACTORS

Careful consideration should be given to the following 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 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 facing us. 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 the Discovery, Development and Commercialization of Our Drugs and Drug Candidates

We depend heavily on the success of XPOVIO® (selinexor). If we are unable to successfully commercialize XPOVIO or successfully develop selinexor for additional indications, or if we experience significant delays in doing so, our business will be materially harmed.

We have invested a significant portion of our efforts and financial resources in the research and development of our lead drug candidate, selinexor. Our ability to generate revenues from the sale of drugs that treat cancer and other diseases in humans will depend heavily on the successful development, regulatory approval and commercialization of selinexor. On July 3, 2019, the U.S. Food and Drug Administration, or FDA, granted accelerated approval for XPOVIO in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma, or RRMM, 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. Our ability to generate product revenues will depend on our successful commercialization of XPOVIO and our obtaining additional marketing approvals for, and successfully commercializing, selinexor for additional indications.

The commercial success of XPOVIO and the successful clinical development of selinexor and our other drug candidates will depend on several factors, including the following:

- successful commercialization of XPOVIO in the United States, including establishing and maintaining sales, marketing and distribution capabilities for XPOVIO;
- 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 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 additional studies that confirm clinical efficacy, effectiveness and safety of XPOVIO and acceptance of the same by the FDA and medical community since continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials;
- acceptance of XPOVIO and, if and when approved, our other drug candidates, by patients, the medical community and third-party payors;
- obtaining and maintaining coverage, adequate pricing and adequate reimbursement by third-party payors, including government payors, for XPOVIO and our drug candidates;
- successful completion of preclinical studies;
- acceptance by the FDA of investigational new drug applications, or INDs, for our drug candidates prior to commencing clinical studies;
- successful enrollment in, and completion of, clinical trials, including demonstration of a favorable risk-benefit ratio;
- receipt of marketing approvals from applicable regulatory authorities;

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- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our drug candidates;
- establishing sales, marketing, manufacturing and distribution capabilities to commercialize any drug candidates for which we may obtain marketing approval, whether alone or in collaboration with others;
- launching commercial sales of any drug candidates for which we obtain marketing approval, whether alone or in collaboration with others;
- effectively competing with other therapies;
- maintaining an acceptable safety profile of the drugs following approval;
- compliance with existing and new health care laws and regulations currently being considered or implemented in the United States, including price reporting and other disclosure requirements of such laws and regulations and the potential impact of such requirements on physician prescribing practices and payor coverage;
- enforcing and defending intellectual property rights and claims; and
- maintaining and growing an organization of scientists and business people, including collaborators, who can develop and commercialize our drug candidates.

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 drug candidates, which would materially harm our business.

The results of previous clinical trials may not be predictive of future results, and the results of our current and planned clinical trials may not satisfy the requirements of the FDA or non-U.S. regulatory authorities.

Clinical failure can occur at any stage of clinical development. Clinical trials may produce negative or inconclusive results, and we or any collaborators may decide, or regulators may require us, to conduct additional clinical trials or preclinical studies. We will be required to demonstrate with substantial evidence through well-controlled clinical trials that our drug candidates are safe and effective for use in a diverse population before we can seek regulatory approvals for their commercial sale. Success in early-stage clinical trials does not mean that future larger registration clinical trials will be successful because drug candidates in later-stage clinical trials may fail to demonstrate sufficient safety and efficacy to the satisfaction of the FDA and non-U.S. regulatory authorities despite having progressed through early-stage clinical trials. Drug candidates that have shown promising results in early-stage clinical trials may still suffer significant setbacks in subsequent registration clinical trials. Additionally, the outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later-stage clinical trials, and interim results of a clinical trial are not necessarily indicative of final results.

In addition, the design of a clinical trial can determine whether its results will support approval of a drug, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We may be unable to design and conduct a clinical trial to support regulatory approval. Further, if our drug candidates are found to be unsafe or lack efficacy, we will not be able to obtain regulatory approval for them and our business would be harmed. A number of companies in the pharmaceutical industry, including those with greater resources and experience than us, have suffered significant setbacks in advanced clinical trials, even after obtaining promising results in earlier clinical trials.

In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same drug 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 rate of dropout 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 sufficient to obtain regulatory approval to market our drug candidates.

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Further, our drug candidates may not be approved even if they achieve their primary endpoints in Phase 3 clinical trials or other registration trials. The FDA or non-U.S. regulatory authorities may disagree with our trial design and our interpretation of data from preclinical studies and clinical trials. In addition, any of these regulatory authorities may change requirements for the approval of a drug candidate even after providing a positive opinion on, or otherwise reviewing and providing comments or advice on, a protocol for a clinical trial that has the potential to result in approval by the FDA or another regulatory authority. In addition, any of these regulatory authorities may also approve a drug candidate for fewer or more limited indications than we request or may grant approval contingent on the performance of costly post-marketing clinical trials. Furthermore, the FDA or non-U.S. regulatory authorities may not approve the labeling claims that we believe would be necessary or desirable for the successful commercialization of our drug candidates.

To date, we have had several discussions with the FDA and non-U.S. regulatory authorities regarding the design of our later phase clinical trials for selinexor, including the BOSTON, STORM, SADAL and SEAL studies. In July 2019, the FDA approved, under accelerated approval based on response rate from the STORM study, XPOVIO in combination with dexamethasone for the treatment of adult patients with RRMM 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. We plan to seek additional regulatory approvals of selinexor in North America and Europe in each indication with respect to which such later phase clinical trial is being conducted and with respect to which we receive positive results that may support full or accelerated approval, as the case may be. We or our current or future partners may also seek such approvals in other geographies. We cannot be certain that we will commence additional later phase trials or complete ongoing later phase trials as anticipated. Before obtaining regulatory approvals for the commercial sale of any drug candidate for a target indication, we must demonstrate with substantial evidence gathered in preclinical studies and well-controlled clinical studies, and, with respect to approval in the United States, to the satisfaction of the FDA, that the drug candidate is safe and effective for use for that target indication. There is no assurance that the FDA or non-U.S. regulatory authorities would consider our current and planned later phase clinical trials to be sufficient to serve as the basis for filing for approval or to gain approval of selinexor for any indication. The FDA and non-U.S. regulatory authorities retain broad discretion in evaluating the results of our clinical trials and in determining whether the results demonstrate that selinexor is safe and effective. If we are required to conduct additional clinical trials of selinexor prior to approval, 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 will need substantial additional funds, and there is no assurance that the results of any such additional clinical trials will be sufficient for approval.

The results to date in preclinical and early clinical studies conducted by us or our academic collaborators and in Phase 1 and Phase 2 clinical trials that we are currently conducting include the response of tumors to selinexor. 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. For example, the primary endpoint of our Phase 2/3 SEAL study, the clinical trial of selinexor in patients with dedifferentiated liposarcoma, and of our Phase 3 BOSTON study, the clinical trial of selinexor in combination with Velcade (bortezomib) and dexamethasone in patients with multiple myeloma, is progression free survival. 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. Overall response rate is defined as the portion of patients with tumor size reduction of a predefined amount for a minimum time period. For some types of cancer, we may use overall response rate as a primary endpoint, as we did in our SADAL study and our STORM study. These clinical trials will not be randomized against control arms and the primary endpoints of these trials are overall response rate. If selinexor does not demonstrate sufficient overall response rates in these indications, or any other indication for which a clinical trial has overall response rate as a primary endpoint, or if the FDA or non-U.S. regulatory authorities do not deem overall response rate a sufficient endpoint, or deem a positive overall response rate to be insufficient, it will

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likely not be approved for that indication based on the applicable study. With respect to the STORM and SADAL studies, the FDA has reiterated to us that it recommends, in general, a randomized trial with a progression-free survival endpoint as an initial registration approach.

Finally, independent review committees are typically implemented to adjudicate efficacy outcomes in clinical studies that are intended to support requests for marketing authorization. For example, in our STORM study, the primary endpoint of overall response rate was determined based on efficacy adjudications by an independent review committee, or IRC, comprised of physicians who are expert in treating and evaluating patients with multiple myeloma. While the FDA agreed with the assessments of the IRC for the STORM study in conducting its review of those data, we cannot be certain that other regulatory authorities will agree with the assessments of the IRC for STORM or any other study for which we may submit data to support a request for marketing authorization.

We may not be successful in our efforts to identify or discover additional potential drug candidates.

Part of our strategy involves identifying and developing drug candidates to build a pipeline of novel drug 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 drug candidates, yet fail to yield drug candidates for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential drug candidates;
- potential drug 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 drug candidates may not be effective in treating their targeted diseases.

Research programs to identify new drug candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on a potential drug candidate that ultimately proves to be unsuccessful.

If we are unable to identify suitable compounds for preclinical and clinical development, we will not be able to obtain revenues from sale of drugs in future periods, which likely would result in significant harm to our financial position and adversely impact our stock price.

Clinical drug development is a lengthy and expensive process, with an uncertain outcome. If clinical trials of our drug 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 drug candidates.

Before obtaining marketing approval from regulatory authorities for the sale of our drug candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our drug candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical studies and early-stage clinical trials may not be predictive of the success of later stage clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, certain data from our Phase 1 and Phase 2 clinical trials of selinexor to date are based on unaudited data provided by our clinical trial investigators. An audit 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. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their drug candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their drug candidates. Furthermore, the

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failure of any drug candidates to demonstrate safety and efficacy in any clinical trial could negatively impact the perception of our other drug candidates and/or cause the FDA or other regulatory authorities to require additional testing before any of our drug 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 or commercialize our drug candidates, including:

- regulatory authorities or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- feedback from regulatory authorities that requires us to modify the design of our clinical trials;
- we may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites or contract research organizations;
- clinical trials of our drug candidates may produce negative or inconclusive results, and we may decide, or regulatory authorities may require us, to conduct additional clinical trials, suspend ongoing clinical trials or abandon drug development programs;
- the number of patients required for clinical trials of our drug candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors, including those manufacturing our drug candidates or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we or our investigators might have to suspend or terminate clinical trials of our drug candidates for various reasons, including non-compliance with regulatory requirements, a finding that our drug candidates have undesirable side effects or other unexpected characteristics, or a finding that the participants are being exposed to unacceptable health risks;
- regulators may recommend or require us to perform additional or unanticipated clinical trials to obtain approval;
- regulators may revise the requirements for approving our drug candidates, or such requirements may not be as we anticipate;
- the cost of clinical trials of our drug candidates may be greater than we anticipate;
- the supply or quality of our drug candidates or other materials necessary to conduct clinical trials of our drug candidates may be insufficient or inadequate;
- regulators may revise the requirements for approving our drug candidates, or such requirements may not be as we anticipate; and
- any partners and collaborators that help 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.

If we are required to conduct additional clinical trials or other testing of our drug candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our drug candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our drug candidates;
- not obtain marketing approval at all;
- 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;

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- 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; or
- have the drug removed from the market after obtaining marketing approval.

Our drug development costs will also increase if we experience delays in testing or marketing approvals. 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. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our drug candidates, allow our competitors to bring drugs to market before we do or impair our ability to successfully commercialize our drug candidates, 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 drug candidates.

If we experience delays or difficulties in the enrollment of patients in clinical trials, or we are otherwise delayed in our ability to conduct clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our drug candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside of the United States. In addition, some of our competitors may have ongoing clinical trials for drug candidates that treat the same indications as our drug candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' drug candidates.

Patient enrollment is affected by other factors, including:

- severity of the disease under investigation;
- availability and efficacy of approved drugs for the disease under investigation;
- patient eligibility criteria for the study in question;
- competing drugs in clinical development;
- perceived risks and benefits of the drug candidate under study;
- restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients.

In addition, patient enrollment may be affected by future regulatory actions, such as Form 483 observations or the partial clinical hold we were subject to previously. In February 2017, following the conclusion of a joint inspection conducted by the FDA and Danish Medicines Agency at our corporate headquarters, the FDA issued a Form 483 noting certain deficiencies in procedures and documentation that were identified in our selinexor development program. We implemented corrective actions, preventative actions and other initiatives directed at resolving the deficiencies identified in the Form 483 observations and provided the FDA with our responses to the Form 483 observations in February 2017.

In addition, in March 2017, the FDA notified us that it had placed the clinical trials under our IND for selinexor on partial clinical hold, which is an order by the FDA to delay or suspend part of a sponsor's clinical

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work requested under its IND as well as investigator-sponsored trials. The partial clinical hold was due to incomplete information in the existing version of the investigator's brochure, including an incomplete list of serious adverse events, or SAEs, associated with selinexor, and not as a result of any new information regarding the safety profile of selinexor. The partial clinical holds on the clinical trials of selinexor were lifted by the FDA Division of Hematology Products (effective March 30, 2017), Division of Oncology Products 1 (effective April 5, 2017) and Division of Oncology Products 2 (effective March 31, 2017). However, if in the future we are delayed in addressing, or unable to address, any concerns of the FDA or other regulators, we could be delayed or prevented from enrolling patients in our clinical trials.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays, could require us to abandon one or more clinical trials altogether and could delay or prevent our receipt of necessary regulatory approvals. Enrollment delays in our clinical trials may result in increased development costs for our drug candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

If serious adverse or unacceptable side effects are identified or we observe limited efficacy of our drug candidates, we may need to abandon or limit the development or commercialization of one or more of our drug candidates, and such findings may delay or prevent regulatory approval, limit commercial viability, or result in significant negative consequences following any marketing approval.

Four of our drug candidates are in clinical development for treatment of human diseases. Their risk of failure is high. If XPOVIO or any of our drug 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 their development or limit development or marketing to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Adverse events, or AEs, in our clinical trials to date have been generally predictable and manageable, although some patients have experienced more serious AEs. The most common drug-related AEs were gastrointestinal, such as nausea, anorexia, diarrhea and vomiting, and fatigue. 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, were thrombocytopenia, or low count of platelets in the blood, and neutropenia, or low neutrophil counts. To date, the most common AEs 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. For example, amongst the 202 patients enrolled in Parts 1 and 2 of the STORM study who were treated with selinexor in combination with dexamethasone, the most common AEs (incidence $\geq 20\%$) were thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infections. The treatment discontinuation rate due to AEs was 27%; 53% of patients had a reduction in the selinexor dose, and 65.3% had the dose of selinexor interrupted. In this group of patients, the most frequent AEs requiring permanent discontinuation in 4% or greater of patients who received selinexor included fatigue, nausea, and thrombocytopenia. Similarly, in the SADAL study, as of April 3, 2019, among the 127 patients included in the safety analysis, the most common AEs (incidence $\geq 20\%$) were thrombocytopenia, nausea, fatigue, anemia, anorexia, diarrhea, constipation, weight loss, neutropenia, vomiting, pyrexia and asthenia. Some patients across our clinical trials have experienced SAEs deemed by us and the clinical investigator to be related to selinexor. SAEs 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.

These AEs and the resulting dose modification and/or treatment discontinuation rates or safety or toxicity issues that we may experience in our clinical trials in the future could result in a more restrictive label for any drug candidates approved for marketing or could result in the delay or denial of approval to market any drug candidates by the FDA or comparable foreign regulatory authorities, which could prevent us from ever generating revenue from the sale of drugs or achieving profitability. Results of our trials could reveal an

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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 to cease further development of or deny approval of our drug 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 drug 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;
- 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.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected drug candidate, if approved, or could substantially increase commercialization costs and expenses, which could delay or prevent us from generating revenues from the sale of our drugs and harm our business and results of operations.

The FDA or non-U.S. regulatory authorities may disagree with our and/or our clinical trial investigators' interpretation of data from clinical trials in determining if serious adverse or unacceptable side effects are drug-related.

We, and our clinical trial investigators, currently determine if serious adverse or unacceptable side effects are drug-related. The FDA or non-U.S. regulatory authorities may disagree with our 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 non-U.S. regulatory authorities may require more information, 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 drug candidates, and/or delay or cause us to change our commercialization plans, or we may decide to abandon the development or commercialization of the drug candidate altogether.

We may expend our limited resources to pursue a particular drug candidate or indication and fail to capitalize on drug candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on research programs and drug candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other drug 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 drugs or profitable market opportunities. Our spending on current and future research and development programs and drug candidates for specific indications may not yield any commercially-viable drugs. If we do not accurately evaluate the commercial potential or target market for a particular drug candidate, we may relinquish valuable rights to that drug 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 drug candidate.

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XPOVIO or any of our drug candidates that receives marketing approval may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

XPOVIO or any of our drug candidates that receive marketing approval may fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Efforts to educate the medical community and third-party payors on the benefits of our drug candidates will require significant resources and may not be successful. For example, current cancer treatments like chemotherapy and radiation therapy are well-established in the medical community, and doctors may continue to rely on these treatments. If XPOVIO or our drug candidates do not achieve an adequate level of acceptance, we may not generate significant revenues from sales of drugs and we may not become profitable. The degree of market acceptance of XPOVIO and our drug candidates, if approved for commercial sale, will depend on a number of factors, including:

- efficacy and potential advantages compared to alternative treatments;
- the ability to offer our drugs for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- sufficient third-party coverage or reimbursement;
- effectiveness of our sales and marketing efforts;
- adverse publicity about our drugs or favorable publicity about competitive products;
- the prevalence and severity of any side effects;
- any restrictions on the use of our drugs together with other medications; and
- inability of certain types of patients to take our drugs.

Our estimates of the potential market opportunities for XPOVIO and our drug 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 drug 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 or maintain profitability.

If we are unable to establish and maintain sales, marketing and distribution capabilities or maintain current agreements or enter into additional sales, marketing and distribution agreements with third parties, we may not be successful in commercializing XPOVIO or any of our drug candidates that we may develop if and when they are approved.

We are in the process of continuing to build and maintain a sales and marketing infrastructure for XPOVIO, our first product, and our company does not have any prior experience in the sales, marketing or distribution of pharmaceutical drugs. To achieve commercial success for any approved drug for which sales and marketing is not the responsibility of any strategic collaborator that we have or may have in the future, we must either develop a sales, marketing and distribution organization or outsource these functions to other third parties. In the future,

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we may choose to build a sales, marketing and distribution infrastructure to market or co-promote one or more of our drug candidates, if and when they are approved, or enter into additional collaborations with respect to the sale, marketing and distribution of our drug candidates. We intend to work with existing and potential partners to establish the commercial infrastructure to support a potential launch of selinexor outside the United States.

There are risks involved with both establishing and maintaining our own sales, marketing and distribution capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time-consuming and could delay any commercial launch of a drug candidate. Further, we may underestimate the size of the sales force required for a successful product launch and may need to expand our sales force earlier and at a higher cost than we anticipated. If the commercial launch of any of our drug candidates for which we establish a commercial infrastructure is delayed or does not occur for any reason, including if we do not receive marketing approval on the timeframe we expect, we would have prematurely or unnecessarily incurred these 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 commercialize XPOVIO or any drug candidates for which we receive marketing approval on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future drugs;
- the lack of complementary drugs to be offered by sales personnel, 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; and
- inability to obtain sufficient coverage and reimbursement from third-party payors and governmental agencies.

Entering into arrangements with third parties to perform sales and marketing services may result in lower revenues from the sale of drug or the profitability of these revenues to us than if we were to market and sell any drugs that we develop ourselves. In addition, we may not be successful in maintaining current arrangements or entering into additional arrangements with third parties to sell, market and distribute XPOVIO or any of our drug candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our drugs effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing XPOVIO or any of our drug candidates for which we obtain marketing approval.

We have a limited number of engagements with specialty pharmacies and specialty distributors. The specialty pharmacies sell XPOVIO directly to patients. The specialty distributors 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 United States, they may not perform as agreed or they may terminate their agreements with us. Also, we may need to enter into agreements with additional pharmacies or distributors, and there is no guarantee that we will be able to do so on 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.

We may not receive royalty or milestone revenue under our partnership agreements for several years, or at all.

Certain of our partnership agreements provide for payments on achievement of development and/or commercialization milestones and for royalties on product sales. However, because drug development entails a

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high risk of failure, we may never realize any material portion of the milestone revenue provided in our partnership agreements and we do not expect to receive any royalty revenue for several years, if at all.

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. We face competition with respect to XPOVIO and our drug candidates and will face competition with respect to any drug candidates that we may seek to discover and develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of major pharmaceutical, specialty pharmaceutical and biotechnology companies that currently market and sell drugs or are pursuing the development of drugs for the treatment of cancer and the other disease indications for which we are developing our drug candidates, although we believe that to date, none of these competitive drugs and therapies currently in development are based on scientific approaches that are the same as our approach. Potential competitors also include academic institutions and governmental agencies and public and private research institutions.

We are initially focused on developing our current drug candidates for the treatment of cancer. 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. We expect that any of our drug candidates that are approved will be priced at a significant premium over competitive generic drugs. This may make it difficult for us to achieve our business strategy of using our drug candidates in combination with existing therapies or replacing existing therapies with our drug candidates.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are more effective, safer, more convenient or less costly than any that we are developing or that would render our drug candidates obsolete or non-competitive. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for their drugs 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 or preventing us from entering into a particular indication at all.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical studies, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs 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 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.

Even if we are able to effectively commercialize XPOVIO or any drug candidate that we may develop, the drugs 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. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or drug licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing

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governmental control even after initial approval is granted. In the United States, approval and reimbursement decisions are not linked directly, but there is increasing scrutiny from the Congress and regulatory authorities of the pricing of pharmaceutical products. 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 drug, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the drug in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more drug candidates, even if our drug candidates obtain marketing approval.

Our ability to effectively commercialize XPOVIO or any of our product candidates that we may develop successfully will depend, in part, on the extent to which reimbursement for these drugs and related treatments will be 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.

A primary trend in the healthcare industry in the United States 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 available for XPOVIO and any drug candidate 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 drug 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 drug candidate for which we obtain marketing approval.

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 United States. 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 United States. 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 drugs and our overall financial condition.

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

We face an inherent risk of product liability exposure related to the testing of our drug candidates in human clinical trials. We face an even greater risk as we commercialize XPOVIO or any other drugs that we may develop. 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 drug candidates or drugs caused injuries, we will incur substantial liabilities or be required to limit commercialization of our drug candidates. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for XPOVIO and any other drugs that we may develop;
- 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 drugs that we may develop.

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 the United States may be adversely affected by international risk and uncertainties.

Although our operations are based in the United States, we conduct business outside the United States 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 the United States. In addition, we plan to seek approvals to sell our products in foreign countries. Any business that we conduct outside the United States will be subject to additional risks that may materially adversely affect our ability to conduct business in international markets, including:

- potentially reduced protection for 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 and regulatory requirements;
- economic weakness, including inflation, volatility in currency exchange rates or political instability in particular foreign economies and markets;
- workforce uncertainty in countries where labor unrest is more common than in the United States;

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- production shortages resulting from any events affecting a product candidate and/or finished drug product supply or manufacturing capabilities abroad;
- business interruptions resulting from geo-political actions, including war and terrorism, 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, or FCPA.

Risks Related to Our Financial Position, Convertible Senior Notes, Revenue Interest Financing Agreement and Need for Additional Capital

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

Since inception, we have incurred significant operating losses. Our net losses were \$199.6 million, \$178.4 million, and \$129.0 million for the years ended December 31, 2019, December 31, 2018 and December 31, 2017, respectively. As of December 31, 2019 and December 31, 2018, we had an accumulated deficit of \$873.3 million and \$673.7 million, respectively. As we only recently launched our first FDA-approved product, XPOVIO, in July 2019, we have had limited revenues to date from product sales and have financed our operations to date 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 and cash generated from our business development activities. We have devoted substantially all of our efforts to research and development, including preclinical studies and clinical trials, pursuing regulatory approvals and engaging in activities to commercially launch XPOVIO for the treatment of adult patients with RRMM 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. Other than the FDA's accelerated approval of XPOVIO, our lead drug candidate, oral selinexor (for indications not yet approved), as well as eltanexor, verdinexor, and KPT-9274, are in clinical development. Although we expect to continue to generate revenue from sales of XPOVIO, there can be no assurance as to the amount or timing of any such revenue, and we expect to continue to incur significant expenses and operating losses. The net losses we incur may fluctuate significantly from quarter to quarter.

We anticipate that our expenses will continue to increase substantially as compared to prior periods as we continue to commercialize XPOVIO in the United States and engage in activities to prepare for the potential commercialization of additional indications for selinexor and the potential approval of our other drug candidates, including due to the impact of increased headcount, to support our clinical and commercialization activities, expanded infrastructure and increased insurance premiums.

We anticipate that our expenses will increase substantially if and as we:

- continue to commercialize XPOVIO in the United States and seek regulatory approval for XPOVIO outside of the United States;
- continue to grow our sales, marketing and distribution infrastructure during the commercialization of XPOVIO and any drug candidates for which we may obtain marketing approval, prior to or upon receiving marketing approval in the United States or outside the United States;
- continue our research and preclinical and clinical development of our drug candidates;
- initiate additional clinical trials for our drug candidates;
- seek marketing approvals for any of our drug candidates that successfully complete clinical trials;
- maintain, expand and protect our intellectual property portfolio;
- manufacture our drug candidates;

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- hire additional clinical, quality control, scientific, commercial and management personnel;
- identify additional drug candidates;
- acquire or in-license other drugs and technologies;
- add operational, financial and management information systems and personnel, including personnel to support our drug development, any commercialization efforts and our other operations as a public company; and
- increase our product liability insurance coverage as we initiate and expand our commercialization efforts.

Our ability to become and remain profitable depends on our ability to commercialize a drug or drugs with significant market potential, either on our own or with a collaborator. 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. This will require us to be successful in a range of challenging activities, including:

- successful launching of XPOVIO, including by further developing our sales force, marketing and distribution capabilities;
- achieving an adequate level of market acceptance and obtaining and maintaining coverage and adequate reimbursement from third-party payors for XPOVIO and any other drugs we commercialize;
- completing preclinical studies and clinical trials of our drug candidates;
- obtaining marketing approval for these drug candidates;
- manufacturing at commercial scale, marketing, selling and distributing XPOVIO or any drug candidates for which we may obtain marketing approval;
- maintaining regulatory and marketing approvals for XPOVIO and for any drug candidates for which we obtain marketing approval;
- establishing and managing any collaborations for the development, marketing and/or commercialization of our drug candidates;
- hiring and building a full commercial organization required for the marketing, selling and distribution for those drugs for which we obtain marketing approval; and
- obtaining, maintaining and protecting our intellectual property rights.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Our expenses could increase if we are required by the FDA or other regulatory authorities to perform clinical trials and non-clinical studies in addition to those that have been conducted or are currently expected, or if there are any delays in the development of any of our drug candidates or the manufacture of any of our drug candidates.

XPOVIO is our only product that has been approved for sale and it has only been approved in the United States for the treatment of adult patients with RRMM 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. Our ability to become and remain profitable will depend, in part, on the timing and success of commercial sales of XPOVIO, which we commercially launched in the United States in July 2019. However, the successful commercialization of XPOVIO in the United States is subject to many risks. We are currently undertaking our first commercial launch with XPOVIO, and we may not be able to do so successfully. There are numerous examples of unsuccessful product launches and failures to meet expectations of market

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potential, including by pharmaceutical companies with more experience and resources than us. We do not anticipate our revenue from sales of XPOVIO alone, in the currently approved indication, will be sufficient for us to become profitable for several years, if at all.

We may never succeed in these activities and 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 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.

The nature and length of our operating history may make it difficult for stockholders to evaluate the success of our business to date and to assess our future viability.

We were incorporated in 2008 and commenced operations in 2009. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our platform, identifying potential drug candidates, conducting preclinical studies and early-phase and later-phase clinical trials of our drug candidates and establishing a commercial infrastructure to launch XPOVIO. We only recently launched XPOVIO and are still in the process of executing our commercial launch plan and, to date, have not generated significant revenue from the sale of XPOVIO. Consequently, any predictions stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

In addition, as a business with a short operating history, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

As we continue to build our business, we expect our financial condition and operating results may fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, stockholders should not rely upon the results of any particular quarterly or annual periods as indications of future operating performance.

We will need substantial additional funding. If we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our research and drug development programs or commercialization efforts.

We expect our expenses to increase in connection with our ongoing activities, particularly as we commercialize XPOVIO (selinexor) and continue the clinical trials of, and seek marketing approval and prepare for commercialization of, selinexor in additional indications and our other drug candidates. Our expenses have increased as we have begun commercializing XPOVIO, including costs associated with our sales force and increased marketing and distribution capabilities. If we obtain marketing approval for any drug candidates that we develop, we expect to incur significant additional commercialization expenses for such drug candidate 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 drug candidate. Furthermore, we will continue to incur additional costs associated with operating as a public company, hiring additional personnel and expanding our facilities. 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 drug development programs or any current or future commercialization efforts.

We expect 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

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statements contained in this Annual Report on Form 10-K. Our future capital requirements will depend on many factors, including:

- our ability to successfully commercialize and sell XPOVIO in the United States;
- the cost of, and our ability to expand and maintain, the commercial infrastructure required to support the commercialization of XPOVIO and any other drug for which we receive marketing approval, including product sales, medical affairs, marketing and distribution;
- the progress and results of our current and planned clinical trials of selinexor;
- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our other drug candidates;
- the costs, timing and outcome of regulatory review of our drug candidates, including whether any additional clinical trials or other activities are required for approval or label expansion;
- our ability to establish and maintain collaborations on favorable terms;
- the success of any collaborations that we have entered into and may enter into with third parties;
- the extent to which we acquire or in-license other drugs and technologies;
- the costs of commercialization activities, including drug sales, marketing, manufacturing and distribution, for any of our drug candidates for which we receive marketing approval, and pre-commercialization costs for our drug candidates incurred prior to receiving any such marketing approval, including the costs and timing of establishing product sales, marketing, manufacturing and distribution capabilities that are not the responsibility of any collaborator that we may have at such time;
- the amount of revenue, if any, received from commercial sales of our drug candidates, assuming receipt of marketing approval;
- the terms and timing of any future collaborations, partnerships, licensing, marketing, distribution or other arrangements that we may establish; 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.

Identifying potential drug candidates, conducting preclinical studies and clinical trials, seeking marketing approvals and commercializing products are time-consuming, expensive and uncertain processes that take years to complete. Although we commercially launched XPOVIO in July 2019, we do not anticipate that our revenue from product sales of XPOVIO will be sufficient for us to become profitable for several years, if at all. In addition, we may never generate the necessary data or results required to obtain marketing approval of our drug candidates. 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. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. Adequate additional financing may not be available to us on acceptable terms, or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate development activities for one or more of our drug candidates or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize XPOVIO or our drug candidates for which we obtain marketing approval.

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 some of the past several years. Such disruptions have resulted, and could in the future result, in diminished liquidity and credit

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availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that any deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be compromised by economic downturns, a volatile business environment and unpredictable and unstable market conditions. 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, which could directly affect our ability to attain our operating goals on schedule and on budget.

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, or 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 Financing Agreement, or Revenue Interest Agreement, that we entered into with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P., or HCR, on September 14, 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 will 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 business may not generate sufficient funds, and we may otherwise be unable to maintain sufficient cash reserves, to pay amounts due under our indebtedness, including the Notes, and our cash needs may increase in the future.

Servicing the Notes will require a significant amount of cash, and we may not have sufficient cash flow from our business to make payments on our indebtedness.

Our ability to pay the principal of or interest and additional interest, if any, 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. If we are unable to generate such cash flow, 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 or engage in these activities on desirable terms, which could result in a default on our debt obligations, including the Notes.

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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 and additional interest, if any. 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. We may not have enough available cash or be able to obtain financing 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. 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 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, or 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, or 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.

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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.

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.

On September 14, 2019, we entered into the Revenue Interest Agreement with 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, 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 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.

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

Until such time, if ever, as we can generate substantial revenues from the sale of drugs, 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 drug 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 drug candidates that we would otherwise prefer to develop and market ourselves.

Risks Related to Our Dependence on Third Parties

We depend on third parties for certain aspects of the development, marketing and/or commercialization of our drug candidates and plan to enter into additional collaborations. If those collaborations are not successful, we may not be able to capitalize on the market potential of these drug candidates.

We intend to maintain our existing collaborations and will continue to seek additional third-party collaborators for certain aspects of the development, marketing and/or commercialization of our drug candidates. For example, we have entered into license arrangements with Ono Pharmaceutical Co., Ltd. and Antengene Therapeutics Limited, and plan to continue to seek to enter into additional license relationships, for marketing and commercialization of selinexor for other geographies outside the United States. In addition, we intend to seek one or more collaborators to aid in the further development, marketing and/or commercialization of our other SINE compounds for indications outside of oncology. Our likely collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. 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 drug candidates. 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.

Collaborations involving our drug 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 drug 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 drug candidate, repeat or conduct new clinical trials or require a new formulation of a drug candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, drugs that compete directly or indirectly with our drugs or drug candidates if the collaborators believe that competitive drugs 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 drugs may not commit sufficient resources to the marketing and distribution of such drug or drugs;
- 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 drug candidates, might lead to additional responsibilities for us with respect to drug 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;

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- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our drugs or drug candidates or that result in costly litigation or arbitration that diverts management's attention and resources of our company;
- 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 drug 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 collaborators or acquirers.

Collaboration agreements may not lead to development or commercialization of drug candidates in the most efficient manner, or at all. If our collaborations do not result in the successful development and commercialization of products 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, our development of our product candidates could be delayed and we may need additional resources to develop product candidates. 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.

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

- not provide us accurate or timely information regarding their inventories, the number of patients who are using XPOVIO or serious adverse reactions, events and/or product complaints regarding XPOVIO;
- not effectively sell or support XPOVIO or communicate publicly concerning XPOVIO in a manner that is contrary to FDA rules and regulations;
- reduce their efforts or discontinue to sell or support or otherwise not effectively sell or support XPOVIO;
- not devote the resources necessary to sell XPOVIO in the volumes and within the 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 and lower product revenue, which would harm our results of operations and business.

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If we are not able to maintain our existing collaborations or establish additional collaborations as we currently plan, we may have to alter our development and commercialization plans and our business could be adversely affected.

Our drug development programs and the commercialization of our drug candidates for which we receive marketing approval will require substantial additional cash to fund expenses. As noted above, we expect to maintain our existing collaborations and collaborate with additional pharmaceutical and biotechnology companies for the development of our drug candidates and the commercialization of our drugs or the potential commercialization of our drug candidates.

We face significant competition in seeking appropriate 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 similar regulatory authorities outside of the United States, the potential market for the subject drug candidate, the costs and complexities of manufacturing and delivering such drug candidate to patients, the potential of competing drugs, 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 drug 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 for our drug candidate.

We may also be restricted under then-existing collaboration agreements from entering into future agreements on certain terms with potential collaborators.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of such drug candidate, reduce or delay its development program or one or more of our other development programs, delay the commercialization of a drug or a drug candidate or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund 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 drug candidates or bring them to market and generate revenue from sales of drugs.

We rely on some 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 contract research organizations, 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 will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that

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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 standards, commonly referred to as Good Clinical Practices, for 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 European Medicines Agency, or 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 drug candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our drug candidates. In such an event, our financial results and the commercial prospects for our drug 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 drug candidates or commercialization of our drugs, producing additional losses and depriving us of potential revenue from sales of drugs.

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

We rely on academic and private non-academic institutions to conduct and sponsor clinical trials relating to selinexor and our other drug candidates. We do not control the design or conduct of the investigator-sponsored trials, and it is possible that the FDA or non-U.S. 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 or execution of the trials or 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 further clinical development of our drug candidates. Further, if investigators or institutions breach their obligations with respect to the clinical development of our drug 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.

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Additionally, the FDA or non-U.S. regulatory authorities may disagree with the sufficiency of our right of reference to 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 non-U.S. 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 contract with third parties for the manufacture of our drug candidates for preclinical studies and clinical trials and expect to continue to do so in connection with the commercialization of XPOVIO and for clinical trials and commercialization of any drug candidates that we develop and commercialize. This reliance on third parties increases the risk that we will not have sufficient quantities of our drug candidates or drugs or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities or personnel. We do not currently have nor do we plan to build internal infrastructure or capability to manufacture XPOVIO or our drug candidates for use in the conduct of our clinical trials or for commercial supply. We currently rely, and expect to continue to rely, on third-party manufacturers for the manufacture of our drug candidates for preclinical studies and clinical trials under the guidance of members of our organization. We have engaged third-party manufacturers for drug substance and drug product services. We do not have a long term supply agreement with any of these third-party manufacturers, and we purchase our required drug supplies on a purchase order basis.

We have engaged a third-party contract manufacturer for the commercial production of XPOVIO and intend to do the same for any drug candidate that is approved by any regulatory agency. Reliance on third-party manufacturers entails risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible failure of the third party to manufacture our drugs or drug candidates according to our schedule, or at all, including if the third-party manufacturer gives greater priority to the supply of other drugs over our drugs and drug 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;
- the possible misappropriation or disclosure by the third party or others of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

This process is difficult and time consuming and we may face competition for access to manufacturing facilities, as there are a limited number of contract manufacturers operating under current Good Manufacturing Practices, or cGMPs, that are capable of manufacturing our drug candidates. Consequently, we may not be able to reach agreement with third-party manufacturers on satisfactory terms, which could delay our commercialization.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the United States. Facilities used by our third-party manufacturers must be inspected by the FDA after we submit an NDA and before potential approval of the drug candidate. Similar regulations apply to manufacturers of our drug candidates for use or sale in foreign countries. We do not control the manufacturing

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process and are completely dependent on our third-party manufacturers for compliance with the applicable regulatory requirements for the manufacture of our drug candidates. If our manufacturers cannot successfully manufacture material that conforms to the strict regulatory requirements of the FDA and any applicable foreign regulatory authority, they will not be able to secure the applicable approval for their manufacturing facilities. If these facilities are not approved for commercial manufacture, we may need to find alternative manufacturing facilities, which could result in delays in obtaining approval for the applicable drug candidate as alternative qualified manufacturing facilities may not be available on a timely basis or at all. In addition, our manufacturers are subject to ongoing periodic unannounced inspections by the FDA and corresponding state and foreign agencies for compliance with cGMPs and similar regulatory requirements. Failure by any of our manufacturers to comply with applicable cGMPs 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 drug candidates and have a material adverse impact on our business, financial condition and results of operations. Any drugs that we may develop may compete with other drug candidates and drugs for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development, marketing approval or commercialization. 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 drug candidates or drugs, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture of XPOVIO or any drug candidates that we develop may adversely affect our future profit margins and our ability to commercialize any drugs that receive marketing approval on a timely and competitive basis.

Risks Related to Regulatory Approval and Marketing of Our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our drug candidates. As a result, we cannot predict when or if we or any of our collaborators will obtain marketing approval to commercialize a drug candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of drugs are subject to extensive regulation by the FDA and comparable foreign regulatory authorities, whose laws and regulations may differ from country to country. We are not permitted to market our drug candidates in the United States or in other countries until we or any of our collaborators receive approval of an NDA from the FDA or marketing approval from applicable regulatory authorities outside of the United States. In July 2019, the FDA approved XPOVIO (selinexor) in combination with dexamethasone for the treatment of adult patients with RRMM 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. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. The ongoing, randomized Phase 3 BOSTON study evaluating selinexor in combination with Velcade[®] (bortezomib) and low-dose dexamethasone may, if successful, serve as the confirmatory trial. In addition, we submitted a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, in January 2019 with a request for conditional approval of selinexor as a treatment for patients with heavily pretreated multiple myeloma based on the results of the STORM study. During March 2019, the EMA had inspectors conduct a Good Clinical Practices, or GCP, inspection at our headquarters, which was also attended by the FDA, as well as inspections of two clinical sites that participated in Part 2 of the STORM study. While we did not receive any findings from the

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FDA, in May 2019, the EMA inspectors provided us a written inspection report seeking our responses to various questions and findings. We promptly addressed the questions and findings in the inspection report and submitted proposals to the EMA's Committee for Medicinal Products for Human Use, or CHMP. In September 2019, we received the Day 180 List of Outstanding Issues from CHMP, which identified two issues requiring resolution. First, CHMP requested that we reconfirm the IRC adjudicated response rate to justify a positive benefit-risk assessment and, second, CHMP requested that we address the findings from the GCP inspection and our corrective measures taken to justify that the clinical trial data are of sufficient quality to support a benefit-risk assessment. In January 2020, we were granted a three-month extension from CHMP to provide additional time to respond to the outstanding questions. We are currently working with CHMP to address the outstanding questions and expect to receive a decision on the application in mid-2020. With the exception of our Supplemental New Drug Application, or sNDA, submission to the FDA requesting approval of selinexor to treat relapsed or refractory diffuse large B-cell lymphoma, or DLBCL, we have not submitted any other application for, or received any marketing approval of, any of our drug candidates in the United States or in any other jurisdiction. We have limited experience in conducting and managing the clinical trials necessary to obtain marketing approvals, including FDA approval of an NDA. The process of obtaining marketing approvals, both in the United States and abroad, is a lengthy, expensive and uncertain process. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the drug candidates involved.

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted drug application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical studies, clinical trials or other studies and testing. In addition, varying interpretations of the data obtained from preclinical studies and clinical trials could delay, limit or prevent marketing approval of a drug candidate. Any marketing approval we or any of our collaborators ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved drug not commercially viable.

Any delay in obtaining or failure to obtain required approvals could materially adversely affect our ability or that of any of our collaborators to generate revenue from the particular drug candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

Since XPOVIO received accelerated approval by the FDA, we must still comply with post-approval development and regulatory requirements to maintain that approval and, if we fail to do so, FDA could withdraw its approval of XPOVIO, which would lead to substantially lower revenues.

For drugs granted accelerated approval, 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. As a condition of the accelerated approval of XPOVIO, we are required to (i) complete and submit a final report with full datasets from the BOSTON study following completion of the study, (ii) conduct a randomized phase 2 clinical trial of selinexor plus dexamethasone with three doses of selinexor including the approved dose of 80 mg on days 1 and 3 of each week and two doses that are lower than the approved dose, in a similar patient population for which XPOVIO is indicated (which we plan to conduct outside the United States), (iii) conduct a trial with selinexor in patients who have mild, moderate or severe hepatic impairment, and (iv) conduct a drug interaction trial with selinexor in patients to evaluate the effect of co-administration of a strong CYP3A4 inhibitor on the pharmacokinetics of selinexor.

The FDA may withdraw approval of a product candidate approved under the accelerated approval pathway if, for example, the trial required to verify the predicted clinical benefit of our product candidate fails to verify such benefit or does not demonstrate sufficient clinical benefit to justify the risks associated with the drug. The FDA may also withdraw approval if other evidence demonstrates that our product candidate is not shown to be

safe or effective under the conditions of use, we fail to conduct any required post approval trial of our product candidate with due diligence or we disseminate false or misleading promotional materials relating to our product candidate. 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/refractory DLBCL, or any other cancer indication.

There can be no assurance that the BOSTON study conducted as part of our post-marketing obligations will confirm that the surrogate marker used for accelerated approval of XPOVIO will eventually show an adequate correlation with clinical outcomes. If the BOSTON study fails to show such adequate correlation, we may not be able to maintain our previously granted marketing approval of XPOVIO.

Our failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad, and any approval we are granted for our product candidates in the United States would not assure approval of product candidates in foreign jurisdictions.

In order to market and sell our drugs in the European Union 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 may differ substantially from that required to obtain FDA approval. The marketing approval process outside of the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside of the United States, 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 United States 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 United States 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 may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Additionally, on June 23, 2016, the electorate in the United Kingdom, or UK, voted in favor of leaving the European Union, commonly referred to as Brexit. Following protracted negotiations, the UK left the European Union on January 31, 2020. Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Discussions between the UK and the European Union have so far mainly focused on finalizing withdrawal issues and transition agreements but have been extremely difficult to date. To date, only an outline of a trade agreement has been reached. Much remains open but the Prime Minister has indicated that the UK will not seek to extend the transitional period beyond the end of 2020. If no trade agreement has been reached before the end of the transitional period, there may be significant market and economic disruption. The Prime Minister has also indicated that the UK will not accept high regulatory alignment with the EU.

Since the regulatory framework for pharmaceutical products in the UK covering quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the UK. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the UK and/or European Union for our product candidates, which could significantly and materially harm our business.

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We may seek approval from the FDA or comparable non-U.S. regulatory authorities to use accelerated development pathways for our product candidates, including for selinexor in diffuse large B-cell lymphoma. If we are not able to use such pathways, we may be required to conduct additional clinical trials beyond those that we contemplate and that would increase the expense of obtaining, and delay the receipt of, necessary marketing approvals, if we receive them at all. In addition, even if we are able to use an accelerated approval pathway, it may not lead to expedited approval of our product candidates, or approval at all.

Under the Federal Food, Drug and Cosmetic Act, or 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 and otherwise evaluate our ability to seek and receive such accelerated approval.

Based on the positive results of the SADAL study, we submitted a sNDA to the FDA in December 2019, with a request for accelerated approval for selinexor as a new treatment for adult patients with relapsed and/or refractory DLBCL, not otherwise specified, who have received at least two prior therapies. The FDA accepted the application for filing on February 18, 2020 and granted Priority Review with a target decision date of June 23, 2020 under the Prescription Drug User Fee Act, or PDUFA. In November 2018, the FDA granted fast track designation to selinexor for this indication. While the FDA agreed that the trial design and indication appear appropriate for accelerated approval, they reiterated to us in their feedback that the availability of accelerated approval will depend on the trial results and available therapies at the time of regulatory action. The FDA also has reiterated to us that it recommends, in general, a randomized trial with a progression-free survival endpoint as an initial registration approach and, for DLBCL, recommended two randomized trials that isolate the treatment effect of selinexor for a DLBCL indication. During a pre-sNDA meeting with the FDA in November 2019, the FDA noted that the sufficiency of efficacy, tolerability and dose optimization data would be a review issue. Although we believe that our SADAL study presents an opportunity for us to request that the FDA grant accelerated approval for selinexor in relapsed and/or refractory DLBCL, there can be no assurance that the FDA will grant such approval, whether on an accelerated basis, or at all.

There can also be no assurance that the FDA will agree with our surrogate endpoints or intermediate clinical endpoints, or that we will decide to pursue or submit any additional NDAs for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that, after feedback from FDA, we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, 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.

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A fast track designation or breakthrough therapy status by the FDA is not assured and, in any event, may not actually lead to a faster development or regulatory review or approval process and, moreover, would not assure FDA approval of our product candidates.

We may be eligible for fast track designation or breakthrough therapy status for product candidates that we develop. If a product is intended for the treatment of a serious or life-threatening disease or condition and the product demonstrates the potential to address unmet medical needs for this disease or condition, the product sponsor may apply for FDA fast track designation. Additionally, a product candidate may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other drugs, 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. The FDA has broad discretion whether or not to grant these designations, so even if we believe a particular product candidate is eligible for such designation or status, the FDA could decide not to grant it. Moreover, even if we do receive such a designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures and there is no assurance that our product candidate will be approved by the FDA.

In April 2018, the FDA granted fast track designation to selinexor for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy that include regimens comprised of an alkylating agent, a glucocorticoid, Velcade[®] (bortezomib), Kyprolis[®] (carfilzomib), Revlimid[®] (lenalidomide), Pomalyst[®] (pomalidomide) and Darzalex[®] (daratumumab) and whose disease is refractory to at least one proteasome inhibitor (Velcade or Kyprolis), one immunomodulatory agent (Revlimid or Pomalyst), glucocorticoids and to Darzalex, as well as to the most recent therapy. In addition, in November 2018, the FDA granted fast track designation to selinexor for the treatment of patients that have relapsed and/or refractory DLBCL after at least two prior multi-agent therapies and who are ineligible for transplantation, including high dose chemotherapy with stem cell rescue. However, even with these fast track designations, we may not experience a faster development process, review or approval compared to conventional FDA procedures and there is no assurance that selinexor will be approved by the FDA for additional indications. For example, in connection with our NDA for XPOVIO, in March 2019, the FDA extended the PDUFA 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 fast track designation. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

Priority review designation by the FDA may not lead to a faster regulatory review or approval process and, in any event, does not assure FDA approval of our product candidate.

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 FDA's goal to review an application is six months, rather than the standard review period of ten months. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily mean a faster regulatory review process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. For example, in connection with our NDA for XPOVIO, in March 2019, the FDA extended the PDUFA 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. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or thereafter.

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

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs and biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may

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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 United States.

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 United States 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 selinexor in acute myeloid leukemia and DLBCL, 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.

On August 3, 2017, Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

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

Once marketing approval has been granted, an approved drug 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 drug candidates for which we or they obtain marketing approval. 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 drugs we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved drugs 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 to monitor and ensure compliance with cGMPs.

Accordingly, assuming we or our current or future collaborators receive marketing approval for one or more of our drug 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, we and our collaborators could have the marketing approvals for our drugs withdrawn by regulatory authorities, and our or our collaborators' ability to market any future drugs 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.

XPOVIO and any of our drug 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 drugs following approval.

XPOVIO and any of our drug 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, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a drug 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, or 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 drug 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, 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 drugs 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 such drugs, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a drug;
- restrictions on drug distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the drugs from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of drugs;
- fines, restitution or disgorgement of profits or revenues;

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- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of drugs;
- drug seizure; or
- injunctions or the imposition of civil or criminal penalties.

Under the Cures Act and the Trump Administration's regulatory reform initiatives, the FDA's policies, regulations and guidance may be revised or revoked and that could prevent, limit or delay regulatory approval of our product candidates, which would impact our ability to generate revenue.

In December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation, but its ultimate implementation is unclear. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump Administration may impact our business and industry. Namely, the Trump Administration has taken several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. An under-resourced FDA could result in delays in the FDA's responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. In January 2017, President Trump issued an executive order, applicable to all executive agencies including the FDA, which requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This executive order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the executive order requires agencies to identify regulations to offset any incremental cost of a new regulation and approximate the total costs or savings associated with each new regulation or repealed regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within OMB in February 2017, the administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. In addition, on February 24, 2017, President Trump issued an executive order directing each affected agency to designate an agency official as a "Regulatory Reform Officer" and establish a "Regulatory Reform Task Force" to implement the two-for-one provisions and other previously issued executive orders relating to the review of federal regulations. It is difficult to predict how these various requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

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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 drug 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 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 REMS with ETASU 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 drug 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 drug candidates, if approved, which could impact our ability to maximize product revenue.

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

In the United States 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 drug 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 drug 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 drugs.

Among the provisions of the Patient Protection and Affordable Care Act, or ACA, of potential importance to our business, including, without limitation, our ability to commercialize and the prices we may obtain for any of our drug candidates that are approved for sale, are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;

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- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (and 70% starting January 1, 2019) point-of-sale discounts off negotiated prices to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in April 2013 and, due to subsequent legislative amendments, will stay in effect through 2029 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for XPOVIO and for any of our product candidates for which we may obtain regulatory approval or the frequency with which XPOVIO or any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal 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.

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, new payment methodologies and additional downward pressure on the price that we receive for XPOVIO or any other approved product and/or the level of reimbursement physicians receive for administering any 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.

Some of the provisions of the ACA have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the Trump Administration to repeal or replace certain aspects of the ACA. Since January 2017, President Trump has signed two executive orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed

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comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or the Tax Act, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the “individual mandate.” 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. The Bipartisan Budget Act of 2018, among other things, amended the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole”. In July 2018, the Centers for Medicare and Medicaid Services, or CMS, published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment.

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 inseparable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The Trump Administration recently represented to the Court of Appeals considering this judgment that it does not oppose the lower court’s ruling. On July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. On December 18, 2019, that 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. On January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. In January 2017, President Trump signed an executive order 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. In October 2017, the President signed a second executive order allowing for the use of association health plans and short-term health insurance, which may provide fewer health benefits than the plans sold through the ACA exchanges. At the same time, the Trump Administration announced that it will discontinue the payment of cost-sharing reduction, or CSR, payments to insurance companies until Congress approves the appropriation of funds for such CSR payments. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. A bipartisan bill to appropriate funds for CSR payments was introduced in the Senate, but the future of that bill is uncertain. Further, in July 2018 following a federal district court decision from New Mexico, the Administration announced that it would be freezing payments to insurers under the ACA to cover sicker patients until it or Congress can address the appropriate methodology for calculating and making such payments. It remains to be seen how this action will affect the implementation of the ACA.

We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provisions. 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

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marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

Further, there have been several recent U.S. congressional inquiries and proposed and enacted federal and 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. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

Specifically, 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. At the federal level, Congress and the current administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the current administration issued a plan to lower drug prices. Under this blueprint for action, the current administration indicated that the Department of Health and Human Services, or HHS, will take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies, advance biosimilars and generics to boost price competition, evaluate the inclusion of prices in drug makers' ads to enhance price competition, speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers, avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid, work to give Medicare Part D plan sponsors more negotiation power with drug makers, examine which Medicare Part B drug prices could be negotiated by Medicare Part D plans, improve the design of the Medicare Part B Competitive Acquisition Program, update Medicare's drug-pricing dashboard to increase transparency, prohibit Medicare Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance, and require that Medicare Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases.

In addition, on December 23, 2019, the Trump Administration published a proposed rulemaking that, if finalized, 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 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, the 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).

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.

Moreover, legislative and regulatory proposals have also been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical drugs. We cannot be sure whether additional

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legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our drug candidates, if any, may be. In addition, increased scrutiny by the Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us and any collaborators to more stringent drug labeling and post-marketing testing and other requirements.

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

Healthcare providers, physicians and third party payors will play a primary role in the recommendation and prescription of any drugs for which we obtain marketing approval. Our future 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 drugs for which we obtain marketing approval. These include the following:

- **Anti-Kickback Statute**—the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- **False Claims Act**—the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at a minimum of \$11,181 and a maximum of \$22,363 per false claim; ;
- **HIPAA**—the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters, and, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms and technical safeguards, with respect to maintaining the privacy, security and transmission of individually identifiable health information;
- **Transparency Requirements**—federal laws require applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and
- **Analogous State and Foreign Laws**—analogous state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, can apply to sales or marketing arrangements and claims involving healthcare items or services and are generally broad and are enforced by many different federal and state agencies as well as through private actions.

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 HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that

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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 expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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

Payments made to physicians in certain European Union 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 European Union Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the European Union 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.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide 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. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the EU General Data Protection Regulation, or the GDPR, which took effect across all member states of the European Economic Area, or EEA, in May 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 increases our obligations with respect to clinical trials conducted in the 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 the European Union, including the United States 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 United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or 20 million Euros, whichever is greater, and it 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. In addition, the GDPR provides that European Union member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with the GDPR's requirements is rigorous and time intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the European Union. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations.

Similar actions are either in place or under way in the United States. 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. The Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act—which went into effect on January 1, 2020—is creating similar risks and obligations as those created by GDPR, though the Act 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). Many other states are considering similar legislation. A broad range of legislative measures also have been introduced at the federal level. Accordingly, failure to comply with federal and state laws (both those currently in effect and future legislation) regarding privacy and security of personal information could expose us to fines and penalties under such laws. There also is the threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our 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 non-U.S. 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 drug candidates outside of the United States and require us to develop and implement costly compliance programs.

We are subject to numerous laws and regulations in each jurisdiction outside the United States 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 United States 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 for international operations. The anti-bribery provisions of the FCPA are enforced primarily by the DOJ. The Securities and Exchange Commission, or SEC, is involved with enforcement of the books and records provisions of the FCPA.

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 are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, 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 United States, 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 drug candidates outside

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of the United States, which could limit our growth potential and increase our development costs. 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.

Governments outside of the United States tend to impose strict price controls, which may adversely affect our revenues from the sales of drugs, if any.

In some countries, including the countries of the European Union, 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 drug to other available therapies. If reimbursement of our drugs is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

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

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

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

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our drug 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 drug 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 United States and other countries with respect to our proprietary drug candidates and other discoveries. We seek to protect our

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proprietary position by filing patent applications in the United States and abroad related to our novel drug candidates and other discoveries that are important to our business. As of February 10, 2020, 73 patents have issued that relate to XPO1 inhibitors, including composition of matter patents for selinexor, verdinexor and eltanexor in the United States, and their use in targeted therapeutics. In addition, 13 patents have issued that relate to our PAK4/NAMPT inhibitors, including two composition of matter patents for KPT-9274 in the United States and its use in targeted therapeutics. We cannot be certain that any other patents will issue with claims that cover any of our key drug candidates or other discoveries or drug candidates.

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 drug 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 United States 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 United States. For example, in some foreign jurisdictions, our ability to secure patents based on our filings in the United States 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 United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our 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 United States, the first to invent the claimed invention was entitled to the patent, while outside of the United States, the first to file a patent application is entitled to the patent. In March 2013, the United States 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, 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 United States 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 discoveries and drug candidates. Given the amount of time required

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for the development, testing and regulatory review of new drug 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 drug 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 drug candidates and technology, including interference proceedings before the U.S. Patent and Trademark Office. 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, drug 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 drug 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 United States Patent and Trademark Office, or 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 drug 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 drug 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 United States, 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 drug candidates in all jurisdictions where these drug candidates are approved, if ever.

If we are unable to obtain a patent term extension for a drug 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 drug 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 drugs, drug 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, contract research organizations, 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 United States 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 10, 2020, we have trademark registrations in the United States 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 United States to register two additional drug names (examination is currently suspended), and KARYFORWARD and a KARYFORWARD logo for our financial aid and charitable services. Outside the United States, XPOVIO is registered or pending in thirty additional jurisdictions, and is registered or pending in Katakana in Japan, Hangul in South Korea, and Chinese characters in Taiwan. 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 United States 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 drug candidates in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark.

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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 drug 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, 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 will also be 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 strategy. 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, our Chief Executive Officer and member of our board of directors, and Dr. Shacham, our President and Chief Scientific Officer, are married to each other. They are two of our executive officers and 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 computer 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 contract research organizations and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, cyber attacks, natural disasters, fire, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our drug development 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 drug candidates could be delayed or halted. We may also be vulnerable to cyber attacks by hackers, or other malfeasance. This type of breach of our cybersecurity may compromise our confidential information and/or our financial information and 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. Moreover, because the techniques used to obtain unauthorized access, disable or degrade service or sabotage systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or to implement adequate security measures.

Risks Related to Our Common Stock

Our executive officers, directors and principal stockholders maintain the ability to control all matters submitted to stockholders for approval.

As of December 31, 2019, our executive officers, directors and a small number of stockholders own more than a majority of our outstanding common stock. As a result, if these stockholders were to choose to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

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;

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- 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.

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

Although our common stock is listed on The Nasdaq Global Select Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for you to sell shares of our common stock without depressing the market price for the shares, or at all. An inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

If securities analysts do not continue to publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

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. There can be no assurance that analysts will provide favorable coverage or continue to cover us. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. 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.

The price of our common stock has been and may be volatile in the future and fluctuate substantially.

Our stock price has been and is likely to be volatile and may fluctuate substantially. For example, since January 1, 2015, our common stock has traded at prices per share as high as \$38.47 and as low as \$3.92. On February 20, 2020, the closing sale price of our common stock on The Nasdaq Global Select Market was \$16.41 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. The market price for our common stock may be influenced by many factors, including:

- our success in launching and commercializing XPOVIO;
- the success of competitive drugs or technologies;
- results of clinical trials of our drug candidates or those of our competitors;
- our success in commercializing our drug candidates, if and when approved;
- regulatory or legal developments in the United States and other countries;

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- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to the commercial launch of XPOVIO and clinical development programs for any of our drug candidates;
- the results of our efforts to discover, develop, acquire or in-license additional drug candidates or drugs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

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

In the past, securities class action litigation has 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. We are a target of this type of litigation. See Part I, Item 3, “Legal Proceedings” in this Annual Report on Form 10-K for information concerning securities litigation recently initiated against us and certain of our executive officers and directors and certain other defendants. We may become the target of additional securities litigation in the future. For example, we may face additional securities class action litigation or other litigation if we fail to successfully launch and commercialize XPOVIO, or if we cannot obtain regulatory approvals for, or if we otherwise fail to successfully commercialize and launch, our drug 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 and cash equivalents and may not use them effectively.

Our management has broad discretion to use our cash and cash equivalents 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 drug 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.

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We have incurred and will continue to incur increased costs as a result of operating as a public company, and our management is required to devote substantial time to compliance initiatives and corporate governance practices.

As a public company, we incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and have made some activities more time-consuming and costly especially since we are no longer an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, and are no longer able to take advantage of certain exemptions from various reporting requirements that are applicable to public companies that are “emerging growth companies” and that were applicable to us prior to January 1, 2019.

Section 404 of the Sarbanes-Oxley Act of 2002 requires us, on an annual basis, to review and evaluate our internal controls. To maintain compliance with Section 404, we are required to document and evaluate our internal control over financial reporting, which has been both costly and challenging. We will need to continue to dedicate internal resources, continue to engage outside consultants and follow a detailed work plan to continue to assess and document the adequacy of internal control over financial reporting, continue to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. There is a risk that in the future neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. A portion of the outstanding shares of our common stock are eligible for sale in the public market under Rule 144 of the Securities Act of 1933, as amended, or the Securities Act, subject to the volume limitations and other conditions of Rule 144. The holders of these shares may at any time decide to sell their shares in the public market. We have also registered all shares of common stock that we may issue under our equity compensation plans. As a result, these shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates, to the extent applicable.

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, or the Code, our net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service (and

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state tax authorities under relevant state tax rules). In addition, as a result of the Tax Act, for U.S. federal income tax purposes, the use of net operating loss carryforwards arising in taxable years beginning after December 31, 2017 is limited to 80% of our taxable income in any future taxable year, although such losses may be carried forward indefinitely. It is uncertain how various states will respond to the Tax Act. 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.

The comprehensive tax reform bill could adversely affect our business and financial condition.

The Tax Act significantly revises the Internal Revenue Code of 1986, as amended. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 34% to a flat rate of 21%, limitation of the tax deduction for net interest expense to 30% of adjusted earnings (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. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain how various states will respond to the Tax Act.

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

We have been named as a defendant in securities class action litigation in the U.S. District Court for the District of Massachusetts. A complaint was filed on July 23, 2019, 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. A second complaint was filed by Heather Mehdi on September 17, 2019, against the same defendants with the exception of the underwriters. The two complaints are related and we expect them to be consolidated by the court. Both complaints allege 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 seek unspecified compensatory damages, including interest; reasonable costs and expenses, including attorneys' and expert fees; unspecified recessionary damages; and such equitable/injunctive relief or other relief as the court may deem just and proper. We have

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reviewed the allegations and believe they are without merit. We intend to defend vigorously against this litigation.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

Our common stock, \$0.0001 par value per share, began trading on the Nasdaq Global Select Market on November 6, 2013, where its prices are quoted under the symbol “KPTI.”

Holders

As of February 14, 2020, there were 6 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.

Business Overview

Overview

We are an innovation-driven pharmaceutical company focused on the discovery, development and commercialization of novel, first-in-class drugs directed against nuclear transport and related targets for the treatment of cancer and other major 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 **Selective Inhibitor of Nuclear Export (SINE)** compounds that inhibit the nuclear export protein exportin 1, or XPO1. These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of high unmet medical need diseases. Our SINE compounds were the first oral XPO1 inhibitors in clinical development. Our lead asset, XPOVIO[®] (selinexor) tablets, was the first SINE compound to receive marketing approval by the U.S. Food and Drug Administration, or FDA, on July 3, 2019 and is currently indicated for use in 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, or PIs, at least two immunomodulatory agents, or IMiDs, and an anti-CD38 monoclonal antibody. We refer to myeloma that is refractory to these five agents as penta-refractory myeloma. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. The ongoing, randomized Phase 3 BOSTON (**B**ortezomib, **S**elinexor and **D**examethasone) study evaluating selinexor in combination with Velcade[®] (bortezomib) and low-dose dexamethasone in patients with myeloma treatment with between one and three prior therapies is expected to serve as the confirmatory trial.

Our focus is on marketing XPOVIO in its currently approved indication 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 conduct additional clinical trials and seek additional approvals for the use of selinexor in combination with other oncology therapies to expand the patient populations that are eligible for selinexor. Thus, we are currently advancing the clinical development of selinexor in multiple hematological malignancies and solid tumor indications. Studies that support submitted applications for regulatory approval include STORM (**S**elinexor **T**reatment of **R**efractory **M**yeloma) and SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma). Ongoing clinical trials evaluating selinexor include the pivotal, randomized Phase 3 BOSTON study in multiple myeloma, the Phase 1b/2 STOMP (**S**elinexor and Backbone **T**reatments of **M**ultiple Myeloma **P**atients) study in combination with standard therapies in multiple myeloma, the Phase 2/3 SEAL (**S**elinexor in **A**dvanced **L**iposarcoma) study in liposarcoma, and the Phase 3 SIENDO (**S**elinexor/Placebo After Combination Chemotherapy **I**n Patients with Advanced or Recurrent **E**NDOMETRIAL Cancer) study evaluating selinexor as maintenance therapy in endometrial cancer. During 2019, final data from the Phase 2b STORM study were published in the *New England Journal of Medicine* (Chari, A. *et al.* August 2019). In addition, we reported updated, positive data from the SADAL study as well as updated interim data for the STOMP study at various medical conferences. As a result of the positive results from STORM, in addition to the FDA approval of our first New Drug Application, or NDA, we also filed a Marketing Authorization Application, or MAA, with the European Medicines Agency, or EMA, in January 2019 and expect to receive a decision on our application in the middle of 2020.

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Based on the positive results of the SADAL study, we submitted a Supplemental New Drug Application, or sNDA, to the FDA in December 2019, with a request for accelerated approval for selinexor as a new treatment for adult patients with relapsed and/or refractory diffuse large B-cell lymphoma, or DLBCL, not otherwise specified, who have received at least two prior therapies. The FDA filed the application on February 18, 2020 and granted Priority Review with a target decision date of June 23, 2020 under the Prescription Drug User Fee Act, or PDUFA. Selinexor has received both Orphan Drug and Fast Track designations from the FDA for this same indication. Provided that marketing approval is granted by the FDA, we expect to be prepared to commercialize selinexor in the United States as a treatment for patients with relapsed and/or refractory DLBCL as early as the middle of 2020. We also plan to submit a MAA to the EMA in 2020 with a request for conditional approval.

In addition to selinexor, we are also advancing a pipeline of novel drug candidates including our other oral SINE compounds eltanexor (KPT-8602) and verdinexor (KPT-335), as well as our oral dual PAK4/NAMPT inhibitor, KPT-9274. We began clinical testing of eltanexor, a second-generation SINE compound, in late 2015. Our clinical development program for eltanexor includes myelodysplastic syndrome, or MDS, colorectal cancer, or CRC, and metastatic castration-resistant prostate cancer, or CRPC. Based on clinical results to date and resource prioritization, we plan to focus on the development of eltanexor in MDS in 2020. We began clinical testing of KPT-9274 in patients with hematologic or solid tumors during 2016 and we plan to study its combination with an anti-PD1 monoclonal antibody in a phase 1 clinical study in the near future. Finally, verdinexor is our lead compound that is being evaluated as a potential therapy for viral, rare disease and autoimmune indications in humans and by a collaborator as a potential therapy for cancers in companion animals.

As of December 31, 2019, we had an accumulated deficit of \$873.3 million. We had net losses of \$199.6 million, \$178.4 million and \$129.0 million for the years ended December 31, 2019, 2018 and 2017, respectively. Net product sales for XPOVIO, which was approved by the FDA in July 2019, were \$30.5 million through December 31, 2019. As we only recently launched XPOVIO, we have had limited revenues to date from product sales and have financed our operations to date principally through private placements of our preferred stock (prior to our initial public offering), proceeds from our initial public offering and follow-on offerings of common stock, issuance of convertible debt, proceeds from a Revenue Interest Financing Agreement (deferred royalty obligation) and cash generated from our business development activities.

We anticipate that our expenses will continue to increase substantially as compared to prior periods as we continue to commercialize XPOVIO in the United States and engage in activities to prepare for the potential commercialization of additional indications for selinexor and the potential approval of our other drug candidates, including due to the impact of increased headcount, to support our clinical and commercialization activities, expanded infrastructure and increased insurance premiums.

We anticipate that our expenses will increase substantially if and as we:

- continue to commercialize XPOVIO in the United States and seek regulatory approval for XPOVIO outside of the United States;
- continue to grow our sales, marketing and distribution infrastructure during the commercialization of XPOVIO and any drug candidates for which we may obtain marketing approval, prior to or upon receiving marketing approval in the United States or outside the United States;
- continue our research and preclinical and clinical development of our drug candidates;
- initiate additional clinical trials for our drug candidates;
- seek marketing approvals for any of our drug candidates that successfully complete clinical trials;
- maintain, expand and protect our intellectual property portfolio;

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- manufacture our drug candidates;
- hire additional clinical, quality control, scientific, commercial and management personnel;
- identify additional drug candidates;
- acquire or in-license other drugs and technologies;
- add operational, financial and management information systems and personnel, including personnel to support our drug development, any commercialization efforts and our other operations as a public company; and
- increase our product liability insurance coverage as we initiate and expand our commercialization efforts.

Financial Overview

Revenue Recognition

We began generating product revenue from the sale of XPOVIO in the United States during the third quarter of 2019. Our ability to continue to generate product revenues will depend on our successful commercialization of XPOVIO and our obtaining additional marketing approvals for, and successfully commercializing, selinexor for additional indications.

Prior to the third quarter of 2019, our revenue was primarily from license arrangements as well as foundation and government grants and contracts.

Cost of Sales

Cost of sales includes the cost of producing and distributing inventories that are related to XPOVIO product revenue in the United States (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 our expectation is that such costs will be recoverable through commercialization of XPOVIO. Prior to the capitalization of XPOVIO inventory costs, such costs were recorded as research and development expenses in the period incurred.

Research and Development Expenses

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

- employee-related expenses, including salaries, benefits, travel and stock-based compensation expense;
- expenses incurred under agreements with third parties, including 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;
- 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

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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 drug 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.

The successful development of our drug candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the remainder of the development of these drug candidates. We are also unable to predict when, if ever, material net cash inflows will commence from any drug candidates. This is due to the numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- establishing an appropriate safety profile with Investigational New Drug-enabling toxicology studies, and ongoing clinical trials;
- successful enrollment in, and completion of, clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our drug candidates;
- establishing commercial sales and marketing capabilities and launching commercial sales of the drugs, if and when approved, whether alone or in collaboration with others; and
- maintaining a continued acceptable safety profile of the drugs following approval.

A change in the outcome of any of these variables with respect to the development of any of our drug candidates would significantly change the costs and timing associated with the development of that drug candidate.

Research and development activities are central to our business model. Drug 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 research and development costs to increase significantly for the foreseeable future as our drug candidates progress in clinical trials. 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 drug 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 will impact our clinical development programs and plans.

Selling, General and Administrative Expenses

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.

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We anticipate that our selling, general and administrative expenses will increase in the future to support continued research and development activities and our commercial operations, especially as it relates to the sales and marketing of XPOVIO. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses.

Interest Expense

Interest expense consists of interest expense related to the aggregate \$172.5 million principal amount of 3.0% Convertible Senior Notes due 2025 that we issued in a private offering to qualified institutional buyers in October 2018 (the Notes) as well as interest expense related to the aggregate \$75.0 million principal amount of the deferred royalty obligation entered into in September 2019 with HealthCare Royalty Partners. A portion of the interest expense on both the Notes and the deferred royalty obligation is non-cash expense relating to the accretion of the value of the debt discount and amortization of issuance costs.

Other Income (Expense)

Other income consists primarily of interest income earned on our cash and cash equivalents and investments. Other expense consists primarily of foreign currency transaction losses associated with our German and Israeli subsidiaries whose functional currency is the Euro and Israeli Shekel, respectively.

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 United States 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 the notes 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 (FASB) 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

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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 United States 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 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).

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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 reduction to accounts receivable.

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 (VA), the Department of Defense (DOD), 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 which 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 experience with similar products in the industry, as well as actuals for 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, product returns, and chargebacks are recorded as reductions of accounts receivable, and distributor fees, government rebates, and other incentives are recorded as a component of accrued expenses. As of December 31, 2019, we have determined a material reversal of revenue would not occur in a future period for the estimates detailed above,

and, therefore, the transaction price was not reduced further during the year ended December 31, 2019. 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, asset purchase 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 such pharmaceutical companies 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 which 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 royalty has been allocated has been satisfied (or partially satisfied).

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing quotations 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. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of 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 expenses 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 on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or 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 for the years ended December 31, 2019 and 2018:

	Years Ended December 31,		
	<u>2019</u>	<u>2018</u> (in thousands)	<u>2017</u>
Revenues:			
Product revenue, net	\$ 30,540	\$ —	\$ —
License and other revenue	10,353	30,336	1,605
Operating expenses:			
Cost of sales	2,407	—	—
Research and development	122,340	161,372	107,273
Selling, general and administrative	105,421	48,847	24,870
Loss from operations	(189,275)	(179,883)	(130,538)
Other (expense) income, net	(10,275)	1,502	1,617
Loss before income taxes	(199,550)	(178,381)	(128,921)
Income tax provision	(40)	(26)	(63)
Net loss	<u>\$ (199,590)</u>	<u>\$ (178,407)</u>	<u>\$ (128,984)</u>

Comparison of Years Ended December 31, 2019 and 2018

Product Revenue, net. We began to record product revenue, net in the third quarter of 2019 following the approval of XPOVIO by the FDA in July 2019 and its subsequent commercial launch in the United States. Product revenue, net for the year ended December 31, 2019 was \$30.5 million.

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License and Other Revenue. License and other revenue for the year ended December 31, 2019 was \$10.4 million compared to \$30.3 million for the year ended December 31, 2018. We recognized \$9.4 million in revenue pursuant to a license arrangement with Antengene Therapeutics Limited, \$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. In comparison, we recognized revenue pursuant to an Asset Purchase Agreement (APA) with Biogen MA Inc. (Biogen) for \$10.0 million and a license arrangement with Ono Pharmaceutical Co., Ltd. (Ono) for \$19.7 million, and \$0.6 million pursuant to a government grant arrangement during the year ended December 31, 2018.

Cost of Sales. Cost of sales includes the cost of producing and distributing inventories that are related to XPOVIO product revenue in the United States 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 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, 2019, we recorded \$2.4 million of cost of sales, including \$1.6 million related to royalties. The cost of sales during the year ended December 31, 2019 only reflects 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, 2019, we have \$2.7 million of this previously expensed XPOVIO and related material on-hand.

Research and Development Expense. Research and development expense decreased by approximately \$39.1 million to \$122.3 million for the year ended December 31, 2019 from \$161.4 million for the year ended December 31, 2018. The decrease was primarily related to:

- a decrease of \$17.5 million in clinical trial costs, primarily related to the selinexor program;
- a decrease of \$11.7 million in consulting and professional costs;
- a decrease of \$9.6 million in personnel costs; and
- a decrease of \$0.9 million in travel costs; offset by
- an increase of \$0.6 million in facility costs and information technology infrastructure costs.

We expect our research and development expenses to increase in 2020 as compared with 2019 as we continue clinical development of selinexor in our lead indications with a focus on regulatory submissions for selinexor.

In addition, based on the positive results of the SADAL study, we submitted an NDA to the FDA with a request for accelerated approval for selinexor as a new treatment for adult patients with relapsed or refractory diffuse large B-cell lymphoma, or DLBCL, not otherwise specified, who have received at least two prior therapies. The FDA accepted the application for filing on February 18, 2020 and granted Priority Review with a target decision date of June 23, 2020 under the Prescription Drug User Fee Act, or PDUFA. We also plan to submit a MAA to the EMA in 2020 with a request for conditional approval.

Selling, General and Administrative Expense. Selling, general and administrative expense increased by approximately \$56.6 million to \$105.4 million for the year ended December 31, 2019 from \$48.8 million for the year ended December 31, 2018. The increase was primarily related to:

- an increase of \$35.9 million in personnel costs, primarily due to increased headcount and related onboarding costs associated with building our commercial team in preparation for and in connection with the U.S. commercial launch of XPOVIO;
- an increase of \$9.4 million in commercial related activities;

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- an increase of \$7.3 million in costs related to corporate training, travel and corporate events; and
- an increase of \$4.3 million in facility costs and information technology infrastructure costs.

We expect our selling, general and administrative expenses to increase in 2020 to support of our expanding operating and commercial activities related to sales and marketing of XPOVIO and any of our drug candidates for which we obtain marketing approval.

Other Income (Expense), Net. Other income (expense), net decreased by approximately \$11.8 million to \$10.3 million in net expense for the year ended December 31, 2019 from \$1.5 million in other income for the year ended December 31, 2018. The net decrease is primarily due to a \$13.2 million increase of interest expense related to the Notes and the deferred royalty obligation offset by a \$1.4 million increase in interest income due to increased returns resulting from a general increase in interest rates and higher investment balances in 2019. We expect interest expense to increase in 2020 and beyond, related to the imputed interest on the deferred royalty obligation.

Comparison of Years Ended December 31, 2018 and 2017

Discussion and analysis of the year ended December 31, 2018 compared to the year ended December 31, 2017 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, 2018 as filed with the SEC on February 28, 2019 (2018 Form 10-K).

Liquidity and Capital Resources

During the third quarter of 2019, we began generating revenues from drug sales, as XPOVIO first became commercially available in the United States in July 2019. We have had limited revenues to date from product sales and have financed our operations principally 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, 2019, our principal source of liquidity was \$264.0 million of cash, cash equivalents and investments. We have had recurring losses and incurred a loss of \$199.6 million for the year ended December 31, 2019. Net cash used in operations for the year ended December 31, 2019 was \$190.8 million. We expect that cash, cash equivalents and investments at December 31, 2019 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.

On September 14, 2019, we entered into a Revenue Interest Financing Agreement (deferred royalty obligation) with HealthCare Royalty Partners III, L.P. and HealthCare Royalty Partners IV, L.P. (HCR). Pursuant to the Revenue Interest Agreement, HCR paid us \$75.0 million (First Investment Amount), less certain transaction expenses, at the initial closing, which occurred on September 27, 2019, as disclosed in Note 15 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.

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In August 2018, we entered into an open market sale agreement (Open Market Sale Agreement) with Jefferies LLC, as agent, relating to an “at the market offering,” pursuant to which we may issue and sell shares of our common stock, having an aggregate offering price of up to \$75.0 million (Open Market Shares). As of February 20, 2020, we had 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 during the year ended December 31, 2019.

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 years ended December 31, 2018 and 2017 combined, we received \$44.6 million in upfront payments under our arrangements with Anivive Lifesciences, Inc., Ono Pharmaceutical Co., Ltd., Biogen MA Inc., and Antengene Therapeutics Limited 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.

Cash flows

The following table provides information regarding our cash flows:

	Years Ended December 31,		
	2019	2018 (in thousands)	2017
Net cash used in operating activities	\$(190,822)	\$(159,117)	\$(73,717)
Net cash provided by (used in) investing activities	78,450	(107,664)	17,108
Net cash provided by financing activities	124,305	316,109	75,743
Effect of exchange rate changes	19	(78)	211
Net increase in cash, cash equivalents and restricted cash	<u>\$ 11,952</u>	<u>\$ 49,250</u>	<u>\$ 19,345</u>

Net Cash Used in Operating Activities

Net cash used in operating activities was \$190.8 million during the year ended December 31, 2019 compared to \$159.1 million during the year ended December 31, 2018. 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 increase in cash used in operating activities during the year ended December 31, 2019 compared to the year ended December 31, 2018 was driven primarily by a \$21.2 million increase in our net loss due to an increase in our operating expenses and changes in the components of working capital.

Net Cash Provided by (Used in) Investing Activities

Net cash provided by investing activities was \$78.5 million during the year ended December 31, 2019, and increased by approximately \$186.1 million compared to \$107.7 million in net cash used in investing activities during the year ended December 31, 2018. The increase was primarily related to an increase of \$119.6 million in the proceeds from maturities of investments, as well as a decrease of \$64.3 million in purchases of investments.

Net Cash Provided by Financing Activities

Net cash provided by financing activities was \$124.3 million during the year ended December 31, 2019 compared to \$316.1 million during the year ended December 31, 2018. The \$191.8 million decrease is primarily

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related to the net proceeds of \$166.9 million from the issuance of the Notes and \$145.7 million from our follow-on offering in May 2018, in comparison to net proceeds of \$73.6 million from the deferred royalty obligation executed with HCR in September 2019 and the net proceeds of \$46.2 million from the sale of Open Market Shares 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, 2017 to the year ended December 31, 2018 can be found in Part II, Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations” of the 2018 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 drug candidates. In addition, we expect to incur significant commercialization expenses related to sales, marketing, manufacturing and distribution of any of our drug 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 drug 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 expect that cash, cash equivalents and short- and long-term investments at December 31, 2019 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 United States and continue the clinical trials of our drug candidates. Our future capital requirements will depend on many factors, including:

- 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 drug candidates;
- the costs of future commercialization activities, including drug sales, marketing, manufacturing and distribution, for any of our drug 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;
- the amount of revenue received from commercial sales of our drug candidates for which we receive marketing approval;
- the progress and results of our current and planned clinical trials of selinexor;
- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our other drug candidates;
- 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 drugs and 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.

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Identifying potential drug candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete. In addition, our drug 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 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

Not applicable.

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 133 through 138 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, 2019.

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 Rules 13a-15(f) and 15d-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, 2019.

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, 2019 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, 2019, 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, 2019, 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 2019 consolidated financial statements of the Company and our report dated February 26, 2020 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 26, 2020

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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 2020 annual meeting of stockholders, pursuant to Regulation 14A of the Exchange Act, which we refer to as our 2020 Proxy Statement. We expect to file our 2020 Proxy Statement with the SEC within 120 days of December 31, 2019.

Item 10. Directors, Executive Officers and Corporate Governance

Information regarding our directors, including the audit committee and audit committee financial experts, and executive officers and compliance with Section 16(a) of the Exchange Act, if applicable, will be included in our 2020 Proxy Statement and is incorporated herein by reference.

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 2020 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 will be included in our 2020 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 2020 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 2020 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.

	<u>Page number</u>
Report of Independent Registered Public Accounting Firm	133
Consolidated Balance Sheets as of December 31, 2019 and 2018	134
Consolidated Statements of Operations for the years ended December 31, 2019, 2018 and 2017	135
Consolidated Statements of Comprehensive Loss for the years ended December 31, 2019, 2018 and 2017	136
Consolidated Statements of Stockholders' Equity for the years ended December 31, 2019, 2018 and 2017	137
Consolidated Statements of Cash Flows for the years ended December 31, 2019, 2018 and 2017	138
Notes to Consolidated Financial Statements	139

(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, 2019 and 2018, 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, 2019, 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, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, 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, 2019, 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 26, 2020 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.

/s/ Ernst & Young LLP

We have served as the Company’s auditor since 2014.
Boston, Massachusetts
February 26, 2020

Karyopharm Therapeutics Inc.
Consolidated Balance Sheets

(in thousands, except share and per share amounts)

	December 31, 2019	December 31, 2018
ASSETS		
Current assets:		
Cash and cash equivalents	\$ 128,858	\$ 118,021
Short-term investments	133,098	210,178
Accounts receivable	7,862	—
Inventory	346	—
Prepaid expenses and other current assets	7,289	6,413
Restricted cash	1,117	—
Total current assets	<u>278,570</u>	<u>334,612</u>
Property and equipment, net	3,046	3,863
Operating lease right-of-use assets	10,617	—
Long-term investments	2,016	2,001
Restricted cash	714	716
Total assets	<u>\$ 294,963</u>	<u>\$ 341,192</u>
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	\$ 985	\$ 4,332
Accrued expenses	40,878	32,493
Deferred revenue	2,341	9,362
Operating lease liabilities	1,646	—
Deferred rent	—	390
Other current liabilities	500	327
Total current liabilities	<u>46,350</u>	<u>46,904</u>
Convertible senior notes	109,857	102,664
Deferred royalty obligation	73,588	—
Operating lease liabilities, net of current portion	13,202	—
Deferred revenue, net of current portion	2,192	4,532
Deferred rent, net of current portion	—	3,922
Total liabilities	<u>245,189</u>	<u>158,022</u>
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Preferred stock, \$0.0001 par value; 5,000,000 shares authorized; none issued and outstanding	—	—
Common stock, \$0.0001 par value; 200,000,000 shares authorized; 65,370,448 and 60,829,308 shares issued and outstanding at December 31, 2019 and 2018, respectively	7	6
Additional paid-in capital	923,142	857,156
Accumulated other comprehensive loss	(37)	(244)
Accumulated deficit	(873,338)	(673,748)
Total stockholders' equity	<u>49,774</u>	<u>183,170</u>
Total liabilities and stockholders' equity	<u>\$ 294,963</u>	<u>\$ 341,192</u>

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

Karyopharm Therapeutics Inc.
Consolidated Statements of Operations

(in thousands, except share and per share amounts)

	For the Years Ended December 31,		
	2019	2018	2017
Revenues:			
Product revenue, net	\$ 30,540	\$ —	\$ —
License and other revenue	10,353	30,336	1,605
Total revenues	<u>40,893</u>	<u>30,336</u>	<u>1,605</u>
Operating expenses:			
Cost of sales	2,407	—	—
Research and development	122,340	161,372	107,273
Selling, general and administrative	105,421	48,847	24,870
Total operating expenses	<u>230,168</u>	<u>210,219</u>	<u>132,143</u>
Loss from operations	(189,275)	(179,883)	(130,538)
Other income (expense):			
Interest income	5,422	4,028	1,698
Interest expense	(15,647)	(2,493)	—
Other expense	(50)	(33)	(81)
Total other (expense) income, net	<u>(10,275)</u>	<u>1,502</u>	<u>1,617</u>
Loss before income taxes	(199,550)	(178,381)	(128,921)
Income tax provision	(40)	(26)	(63)
Net loss	<u>\$ (199,590)</u>	<u>\$ (178,407)</u>	<u>\$ (128,984)</u>
Net loss per share—basic and diluted	<u>\$ (3.22)</u>	<u>\$ (3.14)</u>	<u>\$ (2.81)</u>
Weighted-average number of common shares outstanding used in net loss per share—basic and diluted	<u>61,955,420</u>	<u>56,799,699</u>	<u>45,899,784</u>

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

Karyopharm Therapeutics Inc.
Consolidated Statements of Comprehensive Loss

(in thousands)

	For the Years Ended December 31,		
	2019	2018	2017
Net loss	<u>\$ (199,590)</u>	<u>\$ (178,407)</u>	<u>\$ (128,984)</u>
Other comprehensive income (loss):			
Unrealized gain (loss) on investments	207	39	(97)
Foreign currency translation adjustment	—	(66)	154
Comprehensive loss	<u>\$ (199,383)</u>	<u>\$ (178,434)</u>	<u>\$ (128,927)</u>

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

Karyopharm Therapeutics Inc.
Consolidated Statements of Stockholders' Equity

(in thousands, except share amounts)

	Common Shares		Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2016	41,887,829	4	528,617	(274)	(366,104)	162,243
Cumulative effect adjustment for adoption of new accounting guidance	—	—	253	—	(253)	—
Vesting of restricted stock	182,496	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	154,623	—	858	—	—	858
Stock-based compensation expense	—	—	20,405	—	—	20,405
Issuance of common stock, net of issuance costs of \$1.1 million	7,308,202	1	74,884	—	—	74,885
Unrealized loss on investments	—	—	—	(97)	—	(97)
Foreign currency translation adjustment	—	—	—	154	—	154
Net loss	—	—	—	—	(128,984)	(128,984)
Balance at December 31, 2017	49,533,150	5	625,017	(217)	(495,341)	129,464
Vesting of restricted stock	113,800	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	656,934	—	3,519	—	—	3,519
Stock-based compensation expense	—	—	17,275	—	—	17,275
Issuance of common stock, net of issuance costs of \$0.2 million	10,525,424	1	145,704	—	—	145,705
Equity component of 2025 Notes	—	—	67,850	—	—	67,850
Equity component of deferred financing costs for 2025 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	60,829,308	\$ 6	\$ 857,156	\$ (244)	\$ (673,748)	\$ 183,170
Vesting of restricted stock	17,500	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	811,281	—	4,505	—	—	4,505
Stock-based compensation expense	—	—	15,291	—	—	15,291
Issuance of common stock, net of issuance costs of \$1.0 million	3,712,359	1	46,190	—	—	46,191
Unrealized gain on investments	—	—	—	207	—	207
Foreign currency translation adjustment	—	—	—	—	—	—
Net loss	—	—	—	—	(199,590)	(199,590)
Balance at December 31, 2019	<u>65,370,448</u>	<u>\$ 7</u>	<u>\$ 923,142</u>	<u>\$ (37)</u>	<u>\$ (873,338)</u>	<u>\$ 49,774</u>

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

Karyopharm Therapeutics Inc.
Consolidated Statements of Cash Flows

(in thousands)

	For the Year Ended December 31,		
	2019	2018	2017
Operating activities			
Net loss	\$ (199,590)	\$ (178,407)	\$ (128,984)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	974	735	713
Net amortization of premiums and discounts on investments	(1,382)	29	1,187
Stock-based compensation expense	15,291	17,275	20,405
Amortization of the value of debt discount and issuance costs	7,193	1,420	—
Change in operating assets and liabilities:			
Accounts receivable	(7,862)	—	—
Inventory	(346)	—	—
Prepaid expenses and other current assets	(868)	(4,663)	342
Operating lease right-of-use assets	1,094	—	—
Accounts payable	(3,301)	(1,380)	909
Accrued expenses and other liabilities	8,512	11,255	10,070
Operating lease liabilities	(1,175)	—	—
Deferred revenue	(9,362)	(8,027)	21,921
Deferred rent	—	2,646	(280)
Net cash used in operating activities	<u>(190,822)</u>	<u>(159,117)</u>	<u>(73,717)</u>
Investing activities			
Purchases of property and equipment	(206)	(2,363)	(62)
Proceeds from maturities of investments	257,145	137,510	115,544
Purchases of investments	(178,489)	(242,811)	(98,374)
Net cash provided by (used in) investing activities	<u>78,450</u>	<u>(107,664)</u>	<u>17,108</u>
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	46,191	145,705	74,885
Proceeds from the exercise of stock options and shares issued under employee stock purchase plan	4,505	3,519	858
Proceeds from deferred royalty obligation, net	73,609	—	—
Net cash provided by financing activities	<u>124,305</u>	<u>316,109</u>	<u>75,743</u>
Effect of exchange rate on cash, cash equivalents and restricted cash	19	(78)	211
Net increase in cash, cash equivalents and restricted cash	11,952	49,250	19,345
Cash, cash equivalents and restricted cash at beginning of period	118,737	69,487	50,142
Cash, cash equivalents and restricted cash end of period	<u>\$ 130,689</u>	<u>\$ 118,737</u>	<u>\$ 69,487</u>
Reconciliation of cash, cash equivalents and restricted cash reported within the consolidated balance sheets			
Cash and cash equivalents	\$ 128,858	\$ 118,021	\$ 68,997
Short-term restricted cash	1,117	—	200
Long-term restricted cash	714	716	290
Total cash, cash equivalents and restricted cash	\$ 130,689	\$ 118,737	\$ 69,487
Supplemental disclosures:			
Cash paid for interest on convertible debt	\$ 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	\$ 2,889	\$ —	\$ —

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

Karyopharm Therapeutics Inc.
Notes to Consolidated Financial Statements

1. Organization and Operations

The Company

We are an innovation-driven pharmaceutical company focused on the discovery, development and commercialization of novel, first-in-class drugs directed against nuclear export and related targets for the treatment of cancer and other major diseases. Our **Selective Inhibitor of Nuclear Export (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.

In July 2019, the U.S. Food and Drug Administration (“FDA”) approved XPOVIO[®] (selinexor) in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (“RRMM”) 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. This indication is approved under accelerated approval based on response rate. Following accelerated approval by the FDA, XPOVIO became commercially available in the United States in July 2019.

As of December 31, 2019, we had an accumulated deficit of \$873.3 million.

We have had limited revenues to date from product sales and have financed our operations principally 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 Revenue Interest Financing Agreement (deferred royalty obligation), and cash generated from our business development activities. We expect to continue to incur significant expenses and operating losses for at least the foreseeable future. We expect that our cash, cash equivalents and investments at December 31, 2019 will be sufficient to fund 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, or decision-making group, 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 major diseases. All of our revenue to date has been derived in the United States. All of our material long-lived assets reside in the United States.

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.

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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, 2019 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 in 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, with unrealized gains or losses included in Accumulated Other Comprehensive Loss, exclusive of other-than-temporary impairment losses, if any. Short-term and long-term investments are composed of corporate debt securities, commercial paper, U.S. government agency securities and certificates of deposit.

Concentrations of Credit Risk and Off-Balance Sheet Risk

Financial instruments which potentially subject us to credit risk consist primarily of cash, cash equivalents and investments. We hold these investments in highly rated financial institutions, and, by policy, limit the amounts of credit exposure to any one financial institution. These amounts at times may exceed federally insured limits. We have not experienced any credit losses in such accounts and do not believe we are exposed to any significant credit risk on these funds. We have no off-balance sheet concentrations of credit risk, 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, 2019 and 2018.

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

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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 composed of money market funds. We measure these investments at fair value. The fair value of cash equivalents is determined based on “Level 1” inputs.

Items classified as Level 2 within the valuation hierarchy consist of commercial paper, corporate debt securities, U.S. government agency securities and certificates of deposit. 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, as discussed further in Note 15, “Long-Term Obligations”, 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 interest and other income (expense), net. The assumptions used in the option pricing Monte Carlo simulation model include: (1) our estimates of the probability and timing of related events; (2) the probability-weighted net sales of XPOVIO and any of our other future products, including worldwide net product sales and upfront payments, milestones and royalties; (3) our risk-adjusted discount rate that includes a company specific risk premium; (4) our cost of debt; (5) volatility; and (6) 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, 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	—
	<u>\$206,494</u>	<u>\$ 71,380</u>	<u>\$ 135,114</u>	<u>\$ —</u>
Financial liability				
Embedded derivative liability	\$ 2,300	\$ —	\$ —	\$ 2,300

The following table presents information about our financial assets that have been measured at fair value at December 31, 2018 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	\$ 76,881	\$ 76,881	\$ —	\$ —
Investments:				
Short-term:				
Corporate debt securities	143,079	—	143,079	—
Commercial paper	43,978	—	43,978	—
U.S. government and agency securities	19,124	—	19,124	—
Certificate of deposit	3,997	—	3,997	—
Long-term:				
Corporate debt securities (one to two year maturity)	2,001	—	2,001	—
	<u>\$289,060</u>	<u>\$ 76,881</u>	<u>\$ 212,179</u>	<u>\$ —</u>

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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, 2019 (in thousands):

	Embedded Derivative Liability
Balance as of December 31, 2018	\$ —
Addition of derivative related to deferred royalty obligation.	2,300
Change in fair value of derivative since issuance	—
Balance as of December 31, 2019	<u>\$ 2,300</u>

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. 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 cost of the assets disposed of and the related accumulated depreciation are eliminated from the balance sheets and any related gains or losses are reflected in the 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.

Deferred Rent

Deferred rent consists of rent escalation payment terms, tenant improvement allowances and other incentives received from landlords related to our operating leases under Financial Accounting Standards Board (“FASB”) Accounting Standards Codification (“ASC”) 840. Rent escalation represents the difference between actual operating lease payments due and straight-line rent expense. Tenant improvement allowances and other incentives were also recorded as deferred rent under ASC 840 through December 31, 2018. Deferred rent and lease incentives are recorded as a reduction to our operating lease right-of-use assets as of December 31, 2019.

Revenue Recognition

We adopted Accounting Standards Update (“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

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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 United States 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 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).

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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 reduction to accounts receivable.

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 ("VA"), the Department of Defense ("DOD"), 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 which 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 experience with similar products in the industry, as well as actuals for 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, product returns, and chargebacks are recorded as reductions of accounts receivable and 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, 2019 and,

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therefore, the transaction price was not reduced further during the year ended December 31, 2019. 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 which 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 royalty has been allocated has been satisfied (or partially satisfied).

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Accounts Receivable

In general, accounts receivable consists of amounts due from customers, net of customer allowances for cash discounts, product returns, 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 that are past due for collectability, and periodically evaluate the creditworthiness of our customers. As of December 31, 2019, we determined an allowance for doubtful accounts was not required based upon our review of contractual payment terms and individual customer circumstances.

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 product ingredient, and drug product. Finished goods include packaged and labelled products. Inventories 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 projected by us, 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 salary related 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 product revenue, net. 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, 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

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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 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, or 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.

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 statement of operations. Net foreign exchange losses of less than \$0.1 million were recorded in other income for the years ended December 31, 2019, 2018 and 2017.

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 foreign tax provision pertains to foreign income taxes due at our German subsidiary which operates on a cost plus profit margin basis.

The Tax Cuts and Jobs Act of 2017 (“TCJA”) resulted in significant changes to the U.S. corporate income tax system. For additional details regarding this act, see Note 14, “Income Taxes”.

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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 at December 31, 2019, 2018 and 2017 (in common stock equivalent shares):

	December 31,		
	2019	2018	2017
Outstanding stock options	9,843,094	8,917,084	7,019,083
Unvested restricted stock units	787,320	25,000	253,100

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 are not convertible as of December 31, 2019, they are not participating securities and they will not have an impact on the calculation of basic earnings or loss per share. Based on our net loss position, there is no impact on the calculation of dilutive loss per share during the year ended December 31, 2019.

Recently Adopted Accounting Standards

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* (“ASU 2016-02”), which supersedes the lease guidance under FASB ASC Topic 840, *Leases*, resulting in the creation of FASB ASC Topic 842, *Leases* (“ASC 842”). The FASB also issued amendments to ASU 2016-02, including ASU 2018-10, *Codification Improvements to Topic 842, Leases* (“ASU 2018-10”) and ASU 2018-11, *Leases (Topic 842) Targeted Improvements* (“ASU 2018-11”), which we collectively refer to as the new leasing standard. In summary, the new leasing standard requires that all lessees (i) recognize, on the balance sheet, liabilities to remit lease payments and right-of-use assets, representing the right to use the underlying asset for the lease term for both finance and operating leases, and (ii) disclose qualitative and quantitative information about its leasing arrangements. We adopted the standard effective January 1, 2019 using the optional transition method under ASU 2018-11 and, therefore, prior period financial information has not been retrospectively adjusted.

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

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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.

As summarized in the table below, the standard had a material impact on our condensed 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 from liabilities to a reduction in our operating lease right-of-use assets. However, the standard did not have a material impact on our consolidated statement of operations and comprehensive loss for the twelve months 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. Please refer to Note 9, "Commitments and Contingencies" for further information.

	January 1, 2019 Prior to ASC 842 Adoption	ASC 842 Adjustment	January 1, 2019 as Adjusted
Consolidated balance sheet data (in thousands):			
Operating lease and right-of-use assets(1)	\$ —	\$ 11,711	\$ 11,711
Deferred rent(2)	\$ 390	\$ (390)	\$ —
Deferred rent non-current(2)	\$ 3,922	\$ (3,922)	\$ —
Operating lease liabilities(3)	\$ —	\$ 1,175	\$ 1,175
Non-current operating lease liabilities(3)	\$ —	\$ 14,848	\$ 14,848

- (1) Represents capitalization of operating lease right-of-use assets, offset by reclassification of deferred rent and tenant incentives to operating lease right-of-use assets.
- (2) Represents reclassification of deferred rent and tenant incentives to operating lease right-of-use assets.
- (3) Represents recognition of operating lease liabilities.

We implemented internal controls to enable the preparation of financial information upon adoption.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation-Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"). ASU 2018-07 largely aligns the accounting for share-based payment awards issued to employees and nonemployees by expanding the scope of Topic 718 to apply to nonemployee share-based transactions, as long as the transaction is not effectively a form of financing. The new guidance was adopted on January 1, 2019 and it did not have a material impact on our consolidated financial statements.

In November 2018, the FASB issued ASU No. 2018-18, *Collaborative Arrangements (Topic 808)—Clarifying the Interaction between Topic 808 and Topic 606* ("ASU 2018-18"). The amendments in ASU 2018-18 clarify that certain transactions between collaborative arrangement participants should be accounted for as revenue under ASC 606, when the collaborative arrangement participant is a customer in the context of a unit of account. The amendments under ASU 2018-18 are effective for interim and annual fiscal periods beginning after December 15, 2019, with early adoption permitted. The amendments in ASU 2018-18 should be applied retrospectively to the date of initial application of ASC 606. We adopted this guidance effective January 1, 2019 using the modified retrospective approach. The adoption of this standard did not have a material impact on our condensed consolidated financial statements, as each of our arrangements detailed below within Note 11, "License and Asset Purchase Agreements," were previously accounted for under ASC 606, not ASC 808, and we have no other arrangements within the scope of ASC 808.

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In December 2019, the FASB issued ASU No. 2019-12, *Simplifying the Accounting for Income Taxes* (“ASU 2019-12”). The ASU removes the exception to the incremental approach for intraperiod allocation of tax expense when a company has a loss from continuing operations and income from other items that are not included in continuing operations, such as income recorded in Other Comprehensive Income. The general rule under ASC 740-20-45-7 is that the tax effect of pretax income or loss from continuing operations should be determined by a computation that does not consider the tax effects of items that are not included in continuing operations (the so-called incremental approach). Previously, companies could consider the impact on a loss from continuing operations of items in discontinued operations or other comprehensive income. However, under the amended guidance, companies should not consider the effect of items outside of continuing operations in calculating the tax effect on continuing operations. The new guidance is effective for public business entities with fiscal years, and the related interim periods, beginning after December 15, 2020. For other entities, the ASU is effective for fiscal years beginning after December 15, 2021, and interim periods within fiscal years beginning after December 15, 2022. The guidance in the ASU may be adopted prior to the effective date. We adopted this guidance effective January 1, 2019. The adoption of this standard did not have a material impact on our condensed consolidated financial statements.

Recently Issued Accounting Standards

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* (“ASU 2016-13”). ASU 2016-13 requires that credit losses be reported as an allowance using an expected losses model, representing the entity’s current estimate of credit losses expected to be incurred. The accounting guidance currently in effect is based on an incurred loss model. For available-for-sale debt securities with unrealized losses, this standard now requires allowances to be recorded instead of reducing the amortized cost of the investment. The amendments under ASU 2016-13 are effective for interim and annual fiscal periods beginning after December 15, 2019. We do not expect the adoption of ASC 2016-13 to 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 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 are effective for interim and annual fiscal periods beginning after December 15, 2019, with early adoption permitted. We do not expect ASU 2018-13 to have a material impact on our consolidated financial statements.

In August 2018, the FASB issued ASU No. 2018-15, *Intangible-Goodwill and Other Internal-Use Software (Subtopic 350-40)* (“ASU 2018-15”). ASU 2018-15 updates guidance regarding accounting for implementation costs associated with a cloud computing arrangement that is a service contract. The amendments under ASU 2018-15 are effective for interim and annual fiscal periods beginning after December 15, 2019, with early adoption permitted. We do not expect the adoption of ASU 2018-15 to have a material impact on our consolidated financial statements.

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3. Property and Equipment, net

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

	Estimated Useful Life Years	December 31,	
		2019	2018
Laboratory equipment	4	\$ 593	\$ 593
Furniture and fixtures	5	654	607
Office and computer equipment	3	598	559
Leasehold improvements	Lesser of useful life or lease term	5,443	5,397
		<u>7,288</u>	<u>7,156</u>
Less accumulated depreciation and amortization		(4,242)	(3,293)
		<u>\$ 3,046</u>	<u>\$ 3,863</u>

Depreciation and amortization expense recorded for the years ended December 31, 2019, 2018, and 2017 was \$1.0 million, \$0.7 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, 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
	<u>\$ 135,121</u>	<u>\$ 37</u>	<u>\$ (44)</u>	<u>\$135,114</u>

The following table summarizes our investments in debt securities, classified as available-for-sale as of December 31, 2018 (in thousands):

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Loss	Fair Value
Short-term:				
Corporate debt securities	\$ 143,254	\$ 3	\$ (178)	\$143,079
Commercial paper	44,001	—	(23)	43,978
U.S. government and agency securities	19,131	10	(17)	19,124
Certificates of deposit	4,000	—	(3)	3,997
Long-term:				
Corporate debt securities (one to two year maturity)	2,007	—	(6)	2,001
	<u>\$ 212,393</u>	<u>\$ 13</u>	<u>\$ (227)</u>	<u>\$212,179</u>

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At December 31, 2019 and December 31, 2018, we held 27 and 79 debt securities, respectively, that were in an unrealized loss position. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2019 and 2018 was \$63.8 million and \$180.6 million, respectively. As of December 31, 2019 we did not have any securities in a continuous unrealized loss position for more than 12 months. As of December 31, 2018, 8 corporate debt securities with a fair value of \$14.9 million had been in a continuous unrealized loss position for more than 12 months. The unrealized losses of less than \$0.1 million related to these corporate debt securities were included in accumulated other comprehensive loss as of December 31, 2018. At December 31, 2018, we did not intend to sell the securities with an unrealized loss position in accumulated other comprehensive income, and it was not likely that we would be required to sell these securities before recovery of their amortized cost basis.

We review investments for other-than-temporary impairment 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. Other-than-temporary impairments of investments are recognized in the consolidated statements of operations if we have experienced a credit loss and have the intent to sell the investment or if it is more likely than not that we will be required to sell the investment before recovery of the amortized cost basis. Evidence considered in this assessment includes reasons for the impairment, compliance with our investment policy, the severity and the duration of the impairment and changes in value subsequent to the end of the period. The unrealized losses at December 31, 2019 and 2018 are attributable to changes in interest rates, and we do not believe any unrealized losses represent other-than-temporary impairments.

5. Inventory

The following table presents our inventory of XPOVIO at December 31, 2019 and 2018 (in thousands):

	<u>December 31, 2019</u>	<u>December 31, 2018</u>
Raw materials and work in process	\$ 273	\$ —
Finished goods	73	—
Total inventory	<u>\$ 346</u>	<u>\$ —</u>

At December 31, 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. At December 31, 2019, we have determined that a reserve related to XPOVIO inventory is not required.

6. Accrued Expenses

Accrued expenses consisted of the following as of December 31, 2019 and 2018 (in thousands):

	<u>December 31,</u>	
	<u>2019</u>	<u>2018</u>
Research and development costs	\$ 13,122	\$ 15,903
Payroll and employee-related costs	13,630	10,103
Professional fees	6,172	4,931
Interest	4,371	—
Other	3,583	1,556
	<u>\$ 40,878</u>	<u>\$ 32,493</u>

7. Related Party Transactions

We paid consulting expenses of \$0.2 million for the years ended December 31, 2019 and 2018, for consulting services with certain related parties, including a family member of management and a board member. At December 31, 2019 and 2018, there was less than \$0.1 million and \$0, respectively, included in accounts payable and accrued expenses due to related parties.

8. Stockholders' Equity

Underwritten Offerings

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.

On April 28, 2017, we completed a follow-on offering under our shelf registration statement on Form S-3 (File No. 333-214489) pursuant to which we issued an aggregate of 3,902,439 shares of common stock at a public offering price of \$10.25 per share. We received net proceeds of approximately \$37.9 million from the offering after deducting the underwriting discount and commissions and offering expenses.

Controlled Equity Offering Sales Agreement

On December 7, 2015, we entered into a Controlled Equity Offering Sales Agreement (as amended on November 7, 2016 and December 1, 2017, the "Sales Agreement") with Cantor Fitzgerald & Co., as sales agent ("Cantor"), pursuant to which we issued and sold through Cantor an aggregate of 9,172,159 shares of our common stock, for net proceeds of approximately \$89.1 million. The Sales Agreement was terminated effective August 12, 2018. Under the Sales Agreement, Cantor sold shares of our common stock by methods deemed to be an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended (the "Securities Act"). We paid Cantor a commission of up to 3.0% of the gross proceeds from the sale of the shares of our common stock pursuant to the Sales Agreement and provided Cantor with customary indemnification and contribution rights.

During the year ended December 31, 2018, we did not sell any shares under the Sales Agreement. During the year ended December 31, 2017, we sold an aggregate of 3,405,763 shares under the Sales Agreement for net proceeds of approximately \$37.0 million.

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 (the "Open Market Shares") from time to time through Jefferies (the "Open Market Offering").

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. 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 the 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

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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, 2019, we sold an aggregate of 3,712,359 Open Market Shares 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, as specified in Note 2, "Recent Accounting Pronouncements." The operating lease cost for the Newton, MA Lease for the year ended December 31, 2019 was \$2.8 million, of which approximately \$0.9 million was charges for CAM.

In addition, we are party to 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 year ended December 31, 2019.

Lease Commitments

As of December 31, 2019, 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):

<u>Years ending December 31,</u>	<u>Future Minimum Payments</u>
2020	\$ 3,200
2021	3,277
2022	3,447
2023	3,718
2024 and thereafter	6,735
Total minimum lease payments	\$ 20,377
Less: present value adjustment	(5,529)
Present value of minimum lease payments	<u>\$ 14,848</u>

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As of December 31, 2019, the remaining lease term on the Newton, MA Lease was 5.8 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, 2019, the discount rate used to calculate the operating lease liability was 11.0%. 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 have been named as a defendant in securities class action litigation in the U.S. District Court for the District of Massachusetts. A complaint was filed on July 23, 2019, 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. A second complaint was filed by Heather Mehdi on September 17, 2019, against the same defendants with the exception of the underwriters. The two complaints are related and we expect them to be consolidated by the court. Both complaints allege 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 seek unspecified compensatory damages, including interest; reasonable costs and expenses, including attorneys' and expert fees; unspecified recessionary damages; 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 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 from the date of approval by the FDA through December 31, 2019 (in thousands):

	<u>Discounts and Chargebacks</u>	<u>Fees, Rebates, and Other Incentives</u>	<u>Returns</u>	<u>Total</u>
Short-term:				
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	<u>\$ 1,002</u>	<u>\$ 1,819</u>	<u>\$ 234</u>	<u>\$ 3,055</u>

Discounts, chargebacks, and returns are recorded as reductions of accounts receivable, and fees, rebates, and other incentives are recorded as a component of accrued expenses.

11. License and Asset Purchase Agreements

Antengene License Agreement

Effective May 23, 2018 (the “Antengene Effective Date”), we entered into a License Agreement (“Antengene License 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 granted Antengene exclusive rights to develop and commercialize, at its own cost, (i) selinexor, our lead, novel, oral Selective Inhibitor of Nuclear Export (“SINE”) compound, (ii) eltanexor, our second-generation oral SINE compound, and (iii) KPT-9274, our first-in-class orally bioavailable small molecule that is a non-competitive dual modulator of PAK4 and NAMPT, each for the diagnosis, treatment and/or prevention of all human oncology indications (the “Oncology Field”), as well as (iv) verdinexor, our lead compound in development for the treatment of viral indications for the diagnosis, treatment and/or prevention of certain human non-oncology indications (the “Non-Oncology Field”) (the “Antengene Licensed Compounds”). We licensed the development and commercial rights to Antengene for selinexor and eltanexor in the Oncology Field in mainland China and Macau and licensed the development and commercial rights to Antengene for KPT-9274 in the Oncology Field and verdinexor in the Non-Oncology Field in mainland China, Taiwan, Hong Kong, Macau, South Korea, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam (the “Antengene Territory”).

Pursuant to the terms of the Antengene License Agreement, we received an upfront payment of \$11.7 million, and could receive up to \$105.0 million in milestone payments if certain development and regulatory goals are achieved and up to \$45.0 million in milestone payments if certain sales milestones are achieved, as well as a high single-digit to low double-digit royalty based on future net sales of the Antengene Licensed Compounds 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 Antengene License 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 Antengene License 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 Antengene License Agreement may be terminated earlier by (i) either party for breach of the Antengene License 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 Antengene arrangement in accordance with ASC 606 and concluded that the contract counterparty, Antengene, is a customer. We identified the following material promises under the contract:

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(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 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 Antengene License 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 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 is 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 amongst the Antengene Combined License Obligations as follows: \$9.4 million for selinexor, \$1.0 million for eltanexor, \$1.1 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.

Upon execution of the Antengene License Agreement, the only fixed component of the transaction price included the \$11.7 million up-front payment owed to us. As referenced above, we are eligible to receive additional payments of up to \$105.0 million in milestone payments if certain development and regulatory goals

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are achieved and up to \$45.0 million in milestone payments if certain sales milestones are achieved, as well as a high single-digit to low double-digit royalty on future net sales of the Antengene Licensed Compounds in the Antengene Territory. In addition, we would receive cost reimbursement in connection with Antengene's election to receive additional clinical supply for the Antengene Licensed Compounds in the future. We expect to receive the next milestone payment under this agreement, which is \$5.0 million, upon the first NDA filing in the Antengene Territory in Multiple Myeloma.

The future development and regulatory milestones and cost reimbursement for providing additional clinical supply of the Antengene Licensed Compounds, both 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, 2019, because the amounts were fully constrained as of December 31, 2019. 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 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.

Through the year ended December 31, 2019, we recognized \$9.4 million in revenue under the Antengene License Agreement, as the Antengene Combined License Obligation for selinexor was satisfied when the initial clinical supply of selinexor was delivered during the second quarter of 2019. Revenue will be recognized for the Antengene Combined License Obligation for eltanexor, the Antengene Combined License Obligation for KPT-9274, and the Antengene Combined License Obligation for verdinexor once our promise to provide initial clinical supply of each of the Antengene Licensed Compounds in the future is fulfilled. We currently expect the initial clinical supplies of KPT-9274, eltanexor and verdinexor to be delivered within twelve months of the balance sheet date of December 31, 2019. Accordingly, and as of December 31, 2019, the remaining \$2.3 million of the upfront payment represents a contract liability, all of which was included in deferred revenue and is classified as a current liability.

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, 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.

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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 United States, 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 United States of a Product in amyotrophic lateral sclerosis 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, 2019. 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.

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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

Effective October 11, 2017 (the “Ono Effective Date”), we entered into a license agreement (the “Ono License Agreement”) with Ono Pharmaceutical Co., Ltd., a corporation organized and existing under the laws of Japan (“Ono”), pursuant to which we granted Ono exclusive rights to develop and commercialize, at its own cost, selinexor and eltanexor, for the diagnosis, treatment and/or prevention of all human oncology indications (the “Ono Field”) in Japan, Republic of Korea, Republic of China (Taiwan) and Hong Kong, as well as in the ten Southeast Asian countries currently comprising the Association of Southeast Asian Nations (the “Ono Territory”) (the “Ono Exclusive License”). Pursuant to the terms of the Ono License Agreement, we received an upfront payment of ¥2.5 billion (US\$21.9 million on the date received), and could receive up to ¥10.15 billion (approximately US\$90.5 million at the exchange rate as of the Ono Effective Date) in milestone payments if certain development and regulatory goals are achieved and up to ¥9.0 billion (approximately US\$80.2 million at the exchange rate as of the Ono Effective Date) in milestone payments if certain sales milestones are achieved, as well as a low double-digit royalty based on future net sales of selinexor and eltanexor in the Ono Territory. In addition, upon Ono’s election and the parties’ full execution of a manufacturing technology transfer plan and satisfaction of other specified conditions (the “Ono Manufacturing Election”), we will grant to Ono non-exclusive rights to manufacture selinexor, eltanexor and products containing such compounds in or outside of the Ono Territory solely for development and commercialization in the Ono Field in the Ono Territory.

As part of the Ono License Agreement, Ono will also have the right to participate in global clinical studies of selinexor and eltanexor and will bear the cost and expense for patients enrolled in clinical studies in the Ono Territory. Ono is responsible for seeking regulatory and marketing approvals for selinexor and eltanexor in the Ono Territory, as well as any development of the products specifically necessary to obtain such approvals. Ono is also responsible for the commercialization of products containing selinexor or eltanexor in the Ono Field in the Ono Territory at its own cost and expense.

Subject to the Ono Manufacturing Election, we will furnish clinical supplies of drug substance to Ono for use in Ono’s development efforts pursuant to a clinical supply agreement between us and Ono, and Ono may elect to have us provide commercial supplies of drug product to Ono pursuant to a commercial supply agreement between us and Ono, in each case the costs of which will be borne by Ono.

The Ono License 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 Ono License Agreement may be terminated earlier by (i) either party for breach of the Ono License Agreement by the other party or in the event of the insolvency or bankruptcy of the other party, (ii) Ono 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 Ono challenges or assists with a challenge to certain of our patent rights.

We assessed this arrangement in accordance with ASC 606 and concluded that the contract counterparty, Ono, is a customer. We identified the following material promises under the contract: (i) the Ono Exclusive License for selinexor and eltanexor, (ii) initial data transfer for selinexor and eltanexor, which consisted of regulatory data compiled by us for the licensed compounds and products as of the Ono Effective Date, (iii) initial clinical supply for selinexor, which consisted of units of clinical supply for Ono to conduct its Phase I Trial, and (iv) an obligation to stand-ready to provide initial clinical supply for eltanexor. 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 Ono, including the (i) additional data transfer for selinexor and eltanexor, which would consist

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of the transfer of additional regulatory data compiled by us for the licensed compounds and products after the Ono Effective Date, (ii) additional clinical supply and related substance supply for selinexor and eltanexor, which would consist of supplying Ono with units and substance of selinexor and eltanexor incremental to the initial clinical supply for selinexor and the obligation to stand-ready to provide initial clinical supply for eltanexor, as noted above, (iii) manufacturing technology transfer and license for selinexor and eltanexor under the Ono Manufacturing Election, as detailed above, and (iv) options for a backup compound, which represents Ono's option to select a replacement compound in the event it elects to discontinue the development of either of the licensed compounds (the "Ono Transfer Options"). The Ono 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 Ono License Agreement. We also identified certain other customer options that would create a manufacturing obligation for us if exercised by Ono, including commercial supply. This option is referred to herein as the "Ono Manufacturing Option." The Ono Manufacturing 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 (i) Ono Exclusive License, initial data transfer, and initial clinical supply for selinexor and (ii) Ono Exclusive License, initial data transfer, and obligation to stand-ready to provide initial clinical supply of eltanexor were not distinct from one another, and must be combined as two separate performance obligations (the "Ono Combined License Obligation for selinexor" and the "Ono Combined License Obligation for eltanexor"). This is because, for both selinexor and eltanexor, Ono requires the initial data transfer and clinical supply to derive benefit from the Ono Exclusive License since we did not grant manufacturing licenses for selinexor and eltanexor at contract inception. We also determined that each of the Ono Transfer Options represents a distinct performance obligation. Based on these determinations, we identified six distinct performance obligations at the inception of the Ono License Agreement, including (i) the Ono Combined License Obligation for selinexor, (ii) the Ono Combined License Obligation for eltanexor, and the four components of the Ono Transfer Options, including (iii) the material right for additional data transfer, (iv) the material right for additional clinical supply and related substance supply, (v) the material right for manufacturing technology transfer and license, and (vi) the material right for the option for a backup compound.

We further determined that the up-front payment of ¥2.5 billion (US\$21.9 million on the date received) constituted the entirety of the consideration included in the transaction price at contract inception, which was allocated to the performance obligations based on our best estimate of their relative stand-alone selling prices. We determined that substantially all of the total standalone selling price in the arrangement is derived from the Ono Combined License Obligation for selinexor and the Ono Combined License Obligation for eltanexor. In connection therewith, we estimated the standalone selling price for each of the material rights within the Ono Transfer Options, and determined that such amounts were insignificant, and, therefore, immaterial for purposes of allocation. Accordingly, we allocated the ¥2.5 billion (US\$21.9 million on the date received) upfront transaction price between the Ono Combined License Obligations as follows: \$19.7 million for selinexor and \$2.2 million for eltanexor. 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.

Upon execution of the Ono License Agreement, the transaction price included only the ¥2.5 billion (US\$21.9 million on the date received) up-front payment owed to us. As referenced above, we are eligible to receive additional payments of up to ¥10.15 billion (approximately US\$90.5 million at the exchange rate as of the Ono Effective Date) based on the achievement by Ono of future specified development and regulatory milestones and up to ¥9.0 billion (approximately US\$80.2 million at the exchange rate as of the Ono Effective Date) based on the achievement by Ono of future specified commercial milestones, as well as a low double-digit royalty based on future net sales of selinexor and eltanexor in the Ono Territory. In addition, we could receive cost reimbursement in connection with our promise to stand-ready to provide initial clinical supply for eltanexor in the future. We expect to receive the next milestone payment under this agreement upon the first licensed product in Multiple Myeloma, of ¥1.5 billion (approximately US\$1.5 million), in Japan.

The future development and regulatory milestones and cost reimbursement for providing initial clinical supply of eltanexor, both of 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, 2019. As part of our evaluation of the constraint, we considered numerous factors, including that receipt of such amounts is outside our control. Separately, any consideration related to sales-based milestones, as well as royalties on net sales upon commercialization by Ono, will be recognized when the related sales occur, as they were determined to relate predominantly to the intellectual property granted to Ono 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.

As the initial clinical supply of selinexor was delivered in April 2018, the Ono Combined License Obligation for selinexor was determined to be fulfilled and revenue of \$19.7 million was recognized during the quarter ended June 30, 2018. The transaction price allocated to the Ono Combined License Obligation for eltanexor will be recognized as revenue once our stand-ready promise to provide initial clinical supply of eltanexor in the future is fulfilled, which is the last remaining undelivered promise associated with the Ono Combined License Obligation for eltanexor. As of December 31, 2019, \$2.2 million of the Ono License Agreement upfront payment is included in deferred revenue and is classified as a non-current liability.

12. Stock-based Compensation

During 2010, we established the 2010 Stock Incentive Plan (the “Plan” or the “2010 Plan”). Under the terms of the Plan, we granted options to our employees, officers, directors, consultants and advisors. The exercise price of each stock option is the fair market value as determined in good faith by the Board of Directors (the Board) at the time each option is granted. We granted service-based options under the Plan, which generally vest as follows: 25% of the shares vest one calendar year from the vesting start date, 2.083% of the shares vest on the first day of each month for the three years thereafter. The options granted under the Plan generally expire in 10 years from the date of grant. We will grant no further stock options or other awards under the 2010 Plan.

In October 2013, the Board adopted and our stockholders approved the 2013 Stock Incentive Plan (the “2013 Plan”). The 2013 Plan became effective immediately prior to the closing of the IPO and 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 January 2019, 2018 and 2017, the number of shares available for issuance under the 2013 Plan was increased by 1,939,393, 1,939,393 and 1,675,513 shares of common stock, respectively. As of December 31, 2019, we had 2,373,779 shares available for issuance under the 2013 Plan.

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

	Year Ended December 31,		
	2019	2018	2017
Research and development	\$ 6,457	\$ 8,686	\$11,208
Selling, general and administrative	8,834	8,589	9,197
Total	<u>\$15,291</u>	<u>\$17,275</u>	<u>\$20,405</u>

Stock Options

The total stock-based compensation expense related to employee and non-employee stock options for the years ended December 31, 2019, 2018 and 2017 was \$12.6 million, \$16.4 million and \$16.7 million, respectively.

The following table summarizes stock option activity for employees and nonemployees:

	Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (year)	Aggregate Intrinsic Value (in thousands)
Options outstanding at December 31, 2018	8,917,084	\$ 13.78	7.4	\$ 8,197
Granted	3,325,390	8.67		
Exercised	(394,358)	7.18		
Forfeited	(2,005,022)	13.36		
Options outstanding at December 31, 2019	<u>9,843,094</u>	\$ 12.40	7.0	\$ 82,134
Options exercisable at December 31, 2019	<u>5,391,153</u>	\$ 14.65	5.6	\$ 39,879

The total intrinsic value of stock options exercised for the years ended December 31, 2019, 2018 and 2017 was \$2.2 million, \$6.0 million and \$0.4 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:

	Years Ended December 31,		
	2019	2018	2017
Volatility	79%-81%	79%-81%	79%-85%
Expected term (in years)	5.5-6.0	5.5-9.8	5.5-9.6
Risk-free interest rate	1.42%-2.58%	2.50%-3.05%	1.76%-2.29%
Dividend	—%	—%	—%

We use the simplified method as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, *Share-Based Payment*, 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 utilize the contractual term for options granted to 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. The expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to us, including early stage of product development and therapeutic focus. For these analyses, we select companies with comparable characteristics to

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ours including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected term of the options. 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, 2019, 2018 and 2017 was \$6.01, \$8.91 and \$7.22 per share, respectively.

At December 31, 2019, the total unrecognized compensation related to unvested employee and non-employee stock option awards granted under the 2013 Plan was \$26.7 million, which we expect to recognize over a weighted-average period of approximately 2.66 years.

Restricted Stock Units

A restricted stock unit (“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 four equal annual installments provided that the employee remains employed with us.

During the year ended December 31, 2019, we granted 1,065,970 shares of RSUs under the 2013 Plan. The following is a summary of RSU activity for the 2013 Plan for the years ended December 31, 2019 and 2018, respectively:

	Number of Shares Underlying RSUs	Weighted-Average Grant Date Fair Value
Unvested at December 31, 2018	25,000	\$ 9.87
Granted	1,065,970	9.25
Forfeited	(286,150)	9.24
Vested	(17,500)	8.96
Unvested at December 31, 2019	<u>787,320</u>	<u>\$ 9.28</u>

The total stock-based compensation expense related to RSUs for the years ended December 31, 2019, 2018 and 2017 was \$1.6 million, \$0.4 million and \$3.4 million, respectively.

As of December 31, 2019, there was \$5.8 million of unrecognized compensation costs related to unvested RSUs, which are expected to be recognized over a weighted average period of 3.12 years.

Employee Stock Purchase Plan

We have an Employee Stock Purchase Plan (“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, 2019, 2018 and 2017, \$1.7 million, \$0.9 million and 0.4 million, respectively, was withheld from employees, on an after-tax basis, in order to purchase 415,257, 98,770 and

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57,582 shares of our common stock, respectively. For the years ended December 31, 2019, 2018 and 2017, we recorded stock-based compensation expense related to the ESPP of \$1.1 million, \$0.4 million and \$0.2 million, respectively. As of December 31, 2019, 404,332 shares of our common stock remained available for issuance under the ESPP. As of December 31, 2019, there was \$0.4 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:

	Years Ended December 31,		
	2019	2018	2017
Volatility	61%-104%	48%-61%	48%-78%
Expected term (in years)	0.5	0.5	0.5
Risk-free interest rate	2.4%-2.5%	1.3%-2.1%	0.5%-1.3%
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 \$1.7 million, \$1.1 million and \$0.6 million to the 401(k) Plan for the years ended December 31, 2019, 2018 and 2017, respectively.

14. Income Taxes

New Tax Legislation

On December 22, 2017, the President of the United States signed into law the Tax Cuts and Jobs Act (“TCJA”). This legislation reduced the U.S. corporate tax rate from the current rate of 34% to 21% for tax years beginning after December 31, 2017. As a result of the enacted law, we were required to revalue deferred tax assets and liabilities existing as of December 31, 2017 from the 34% federal rate in effect through the end of 2017, to the new 21% rate. We have recognized the impact of the TCJA in these consolidated financial statements and related disclosures. In the year ended December 31, 2018, we recorded an impact of \$0.5 million related to the return to provision items for federal rate change, which is offset by a full valuation allowance. The impact of the remeasurement of our U.S. deferred tax assets and liabilities to 21% resulted in the reduction of deferred tax assets of approximately \$42.7 million, which is offset by a full valuation allowance. There was no impact to our income statement due to the reduction in the U.S. corporate tax rate.

Income Taxes

For the years ended December 31, 2019, 2018 and 2017, we recorded an income tax expense of less than \$0.1 million for our operations in Germany. Our foreign tax provision pertains to foreign income taxes due at our German subsidiary which operates on a cost-plus profit margin.

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

	Year Ended December 31,		
	2019	2018	2017
Foreign	\$ (23,350)	\$ (28,689)	\$ (35,680)
U.S.	(176,200)	(149,692)	(93,241)
Totals	<u>\$ (199,550)</u>	<u>\$ (178,381)</u>	<u>\$ (128,921)</u>

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,	
	2019	2018
Deferred tax assets:		
U.S. and state net operating loss carryforwards	\$ 150,909	\$ 116,236
Stock-based compensation	11,914	11,228
Accruals and other temporary differences	4,212	3,605
Research and development credits	62,374	49,307
Capitalized research and development	1,021	1,388
Fixed assets and intangibles	5,893	6,422
Deferred revenue	1,051	527
Foreign net operating loss carryforwards	4	72
Lease liability	3,443	—
Deferred royalty embedded derivative	533	—
Valuation allowance	(224,943)	(173,247)
Total deferred tax assets	<u>16,411</u>	<u>15,538</u>
Deferred tax liabilities:		
Convertible debt amortization	(13,431)	(15,538)
Right-of-use asset	(2,462)	—
Deferred royalty obligation	(518)	—
Total deferred tax liabilities	<u>(16,411)</u>	<u>(15,538)</u>
Net deferred tax assets	<u>\$ —</u>	<u>\$ —</u>

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, 2019 and 2018. The valuation allowance increased approximately \$51.7 million during the year ended December 31, 2019 to \$224.9 million, from \$173.2 million during the year ended December 31, 2018, primarily due to the generation of net operating losses.

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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,		
	2019	2018	2017
Federal income tax expense at statutory rate	21.0%	21.0%	34.0%
State income tax, net of federal benefit	1.7%	0.7%	5.9%
Permanent differences	(0.5)%	— %	(3.9)%
Research and development credit	6.0%	7.8%	8.4%
Foreign rate differential	(2.5)%	(3.4)%	(9.4)%
Change in valuation allowance	(25.9)%	(28.2)%	(1.4)%
Provision to return adjustments	0.6%	2.4%	1.0%
Other	(0.4)%	(0.6)%	(1.4)%
Federal rate change	—%	0.3%	(33.2)%
Effective income tax rate	—%	—%	—%

As of December 31, 2019 and 2018, we had U.S. federal net operating loss carryforwards of approximately \$576.5 million and \$427.0 million, respectively, which may be able to offset future income tax liabilities. Of the \$576.5 million carryforward as of December 31, 2019, \$283.6 million of the carryforward has an indefinite life and \$292.9 million will expire at various dates through 2037. As of December 31, 2019 and 2018, we had U.S. state net operating loss carryforwards of approximately \$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 2039. Also as of December 31, 2019, we had foreign net operating loss carryforwards of less than \$0.1 million, which have an indefinite life and may be able to offset future foreign income tax liabilities.

As of December 31, 2019 and 2018, we had federal research and development tax credit carryforwards of approximately \$58.5 million and \$46.9 million, respectively, available to reduce future tax liabilities, which expire at various dates through 2039. As of December 31, 2019 and 2018, we had state research and development tax credit carryforwards of approximately \$4.9 million and \$3.0 million, respectively, available to reduce future tax liabilities, which expire at various dates through 2034. We completed a study of R&D tax credits through December 31, 2018 and adjusted our deferred tax asset for the result of that study. For the year ending December 31, 2019, 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 resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code. We completed a Section 382 analysis through July 31, 2015 and subsequently reduced our deferred tax assets for tax attributes we believe will expire unused. We updated our Section 382 analysis through December 31, 2019 and confirmed there were no ownership changes since July 31, 2015. 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.

In October 2016 the FASB issued ASU 2016-16. This standard eliminates the deferral of the tax effects of intra-entity asset transfers other than inventory. As a result, the income tax consequences from the intra-entity transfer of an asset other than inventory and associated changes to deferred taxes will be recognized when the transfer occurs. We adopted this standard on January 1, 2018, using the modified retrospective method, through a cumulative-effect adjustment to retained earnings as of that date. Upon adoption, we recognized additional deferred tax assets of approximately \$19.2 million which were offset by a corresponding valuation allowance.

We will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 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 United States, and various state and foreign jurisdictions. The federal, state and foreign income tax returns are generally subject to tax examinations for the tax years ended December 31, 2016 through December 31, 2019. 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 our 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 convertible 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).

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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, 2019, 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, 2019 consisted of the following (in thousands):

Liability component:	
Principal	\$ 172,500
Less: debt discount and issuance costs, net	(62,643)
Net carrying amount	<u>\$ 109,857</u>
Equity component:	<u>\$ 65,641</u>

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, 2019, the "if-converted value" did not

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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, 2019 was approximately \$251.0 million.

The following table sets forth total interest expense recognized related to the Notes during the year ended December 31, 2019 (in thousands):

	Year Ended December 31, 2019
Contractual interest expense	\$ 5,175
Amortization of debt discount	6,849
Amortization of debt issuance costs	344
Total interest expense	<u>\$ 12,368</u>

Future minimum payments on the Notes as of December 31, 2019 were as follows (in thousands):

Years ended December 31,	Future Minimum Payments
2020	\$ 5,175
2021	5,175
2022	5,175
2023	5,175
2024 and thereafter	182,850
Total minimum payments	\$ 203,550
Less: interest	(31,050)
Less: unamortized discount	(62,643)
Less: current portion	—
Convertible senior notes	<u>\$ 109,857</u>

Deferred Royalty Obligation

In September 2019, we entered into a Revenue Interest Financing Agreement (“deferred royalty obligation”) 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 a tiered royalty 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 HCR up to such minimum amounts.

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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 United States 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. The aggregate fair value of the embedded derivative at issuance date is included in deferred royalty obligation. 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, 2019 was 18.4%. 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 as of December 31, 2019 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, 2019 was \$71.3 million based on \$75.0 million of proceeds, net of fair value of the bifurcated embedded derivative liability and debt issuance costs incurred. The carrying value of the deferred royalty obligation approximates fair value at December 31, 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.

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	Amended and Restated By-Laws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on November 18, 2013)
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	Third Amended and Restated Investors' Rights Agreement dated as of July 26, 2013 (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)
4.3	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)
4.4**	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*	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)

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<u>Exhibit Number</u>	<u>Description of Exhibit</u>
10.9*	<u>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).</u>
10.10*	<u>Managing Director Agreement, dated October 15, 2014, by and between Karyopharm Europe GmbH and Ran Frenkel (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 13, 2015).</u>
10.11*	<u>Letter Agreement, dated October 15, 2014, by and between the Registrant and Ran Frenkel (incorporated by reference to Exhibit 10.17 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 13, 2015).</u>
10.12*	<u>Amended and Restated Letter Agreement, dated as of January 23, 2015, 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 January 23, 2015).</u>
10.13*	<u>Amended and Restated Letter Agreement, dated as of January 23, 2015, 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 January 23, 2015).</u>
10.14*	<u>Amendment to Managing Director Agreement, dated February 15, 2015, by and between Karyopharm Europe GmbH and Ran Frenkel (incorporated by reference to Exhibit 10.22 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 13, 2015).</u>
10.15*	<u>Offer Letter, dated June 7, 2015, between the Registrant and Ran Frenkel (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 June 10, 2015).</u>
10.16*	<u>First Amendment to Letter Agreement, dated October 4, 2016, between the Registrant and Ran Frenkel (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 16, 2017).</u>
10.17*	<u>Amended and Restated Letter Agreement, dated as of September 18, 2015, between the Registrant and Christopher B. Primiano (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 9, 2015).</u>
10.18*	<u>Amendment to Managing Director Agreement, dated October 16, 2015, between Karyopharm Europe GmbH and Ran Frenkel (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 November 9, 2015).</u>
10.19*	<u>Offer Letter, dated September 9, 2017, between the Registrant and Michael Falvey (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 12, 2017).</u>
10.20*	<u>Offer Letter, dated June 7, 2018, between the Registrant and Anand Varadan (incorporated by reference to Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on August 7, 2018).</u>
10.21*	<u>Separation Agreement dated as of January 17, 2019, between the Registrant and Michael Falvey (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 18, 2019).</u>

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<u>Exhibit Number</u>	<u>Description of Exhibit</u>
10.22*	<u>Consulting Agreement, dated as of January 18, 2019, between the Registrant and Michael Falvey (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 January 18, 2019)</u>
10.23*	<u>Nonstatutory Stock Option Agreement, dated September 9, 2017, between the Registrant and Michael Falvey (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 12, 2017)</u>
10.24	<u>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)</u>
10.25	<u>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)</u>
10.26	<u>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)</u>
10.27	<u>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)</u>
10.28	<u>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)</u>
10.29†	<u>Research Agreement, dated as of July 18, 2011, between the Registrant and the Multiple Myeloma Research Foundation, Inc. (incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)</u>
10.30	<u>Open Market Sale AgreementSM, 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)</u>
10.31†	<u>License Agreement, dated October 11, 2017, by and between the Registrant and Ono Pharmaceutical Co., Ltd. (incorporated by reference to Exhibit 10.30 to the Registrant's Annual Report on Form 10-K (File No. 001-36167) filed with the Commission on March 15, 2018)</u>
10.32†	<u>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)</u>
10.33†	<u>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)</u>

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<u>Exhibit Number</u>	<u>Description of Exhibit</u>
10.34	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)
10.35*	Offer Letter, dated February 3, 2019, between the Registrant and Michael Mason (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on February 25, 2019)
10.36*	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)
10.37*	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.

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- * 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.

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” or “we”), 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 4.4 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.

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.

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 and 333-229971) pertaining to the 2013 Stock Incentive Plan of Karyopharm Therapeutics Inc. and 2013 Employee Stock Purchase Plan of Karyopharm Therapeutics Inc.;
4. Registration Statement (Form S-3, File No. 333-226038) 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.; and
6. Registration Statement (Form S-8, File No. 333-233094) pertaining to Inducement Stock Option Awards (August 2018 - July 2019) of Karyopharm Therapeutics Inc.;

of our reports dated February 26, 2020, 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, 2019.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 26, 2020

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 26, 2020

/s/ Michael G. Kauffman

Michael G. Kauffman, M.D., Ph.D.

Chief Executive Officer

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 26, 2020

/s/ Michael Mason

Michael Mason

Senior Vice President, Chief Financial Officer and Treasurer

(Principal Financial and Accounting Officer)

**CERTIFICATIONS 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, 2019, 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 26, 2020

/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)*