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

FORM 10-K

(Mark One)

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

For the fiscal year ended: December 31, 2017

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

For the transition period from _____ to _____

Commission file number: 001-36167

KARYOPHARM THERAPEUTICS INC.
(Exact name of registrant as specified in its charter)

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

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

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

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

(Title of each class)	**(Name of each exchange on which listed)**
Common Stock, $0.0001 par value	**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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

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

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐
		Emerging growth company	☒

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

Indicate by check mark whether the registrant 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, 2017 was approximately $316,146,057. 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 March 9, 2018: 49,652,828.

Documents incorporated by reference:

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 30, 2018 in connection with our 2018 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 collaborations with third parties, our future operating results and financial position, our business strategy, and other objectives for future operations. We often use words such as "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify these forward-looking statements by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause actual results or events to differ materially from those indicated by forward-looking statements. These risks and uncertainties include those inherent in pharmaceutical research and development, such as 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 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 a clinical-stage pharmaceutical company focused on the discovery, development and subsequent 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 focused on understanding the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing wholly-owned, novel, small molecule **S**elective **I**nhibitor of **N**uclear **E**xport (**SINE**) compounds that inhibit the nuclear export protein exportin 1 (XPO1). These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases in areas of unmet medical need. Our SINE compounds were the first oral XPO1 inhibitors in clinical development.

Our focus is on seeking the regulatory approval and commercialization of our lead drug candidate, selinexor (KPT-330), as an oral agent in cancer indications with significant unmet clinical need, initially for hematologic malignancies. We then plan to seek additional approvals for the use of selinexor in combination therapies to expand the patient populations that are eligible for selinexor, as well as to move selinexor towards front-line cancer therapy. We are also advancing the clinical development of selinexor in multiple solid tumor indications. To date, over 2,200 patients have been treated with oral selinexor in company- and investigator-sponsored clinical trials in advanced hematologic malignancies and solid tumors. Selinexor is currently being evaluated in several later-stage clinical trials, including, among others, the Phase 2b STORM (**S**elinexor **T**reatment **o**f **R**efractory **M**yeloma) study in multiple myeloma, the Phase 1b/2 STOMP (**S**elinexor and Backbone **T**reatments **o**f **M**ultiple Myeloma **P**atients) study in combination with standard therapies in multiple myeloma, the Phase 2b SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study in diffuse large B-cell lymphoma (DLBCL), the pivotal, randomized Phase 3 BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**one**) study in multiple myeloma, and the Phase 2/3 SEAL (**Se**linexor in **A**dvanced **L**iposarcoma) study in liposarcoma.

We expect to provide top-line data from the expanded cohort for the STORM study at the end of April 2018, top-line data from the SADAL study by the end of 2018, top-line data from the BOSTON study in 2019 and top-line data from the Phase 3 portion of the SEAL study by the end of 2019. We are also establishing the commercial infrastructure to support a potential launch of selinexor in the United States and we intend to work with existing and potential partners to establish such commercial infrastructure outside the United States. In October 2017, we entered into an exclusive license agreement with Ono Pharmaceutical Co., Ltd. for the development and commercialization of selinexor and eltanexor (KPT-8602) for all human oncology indications in Japan, South Korea, Taiwan, Hong Kong, and the ten Southeast Asian countries currently comprising the Association of Southeast Asian Nations (ASEAN).

Summary of Clinical Development

Oral selinexor is being evaluated in multiple later-phase clinical trials in patients with relapsed and/or refractory hematological and solid tumor malignancies. 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. To date, oral selinexor has been administered to more than 2,200 patients across company- and investigator-sponsored clinical trials; the vast majority of these patients have very heavily pretreated, relapsed or refractory disease. Evidence of single-agent anti-cancer activity has been observed in many patients and selinexor has been sufficiently well-tolerated to allow several of these patients to remain on therapy for prolonged periods. Over 50 patients have remained on study for over 12 months, with several patients on study for over 24 months.

During 2016 and 2017, we reported several important clinical data sets for selinexor and communicated our plan to pursue a clinical development initiative focused on obtaining our first regulatory approval for selinexor in multiple myeloma. This strategy is based on the positive interim results reported to date from the ongoing Phase 2b STORM study and the ongoing Phase 1b/2 STOMP study. The STORM study is a single-arm clinical trial evaluating oral selinexor in combination with standard, low-dose dexamethasone in patients with penta-refractory myeloma. Patients with penta-refractory myeloma have received several previous treatments, including with alkylating agents, glucocorticoids, two immunomodulatory drugs (IMiDs), specifically Revlimid® (lenalidomide) and Pomalyst® (pomalidomide), and two proteasome inhibitors (PIs), specifically Velcade® (bortezomib) and Kyprolis® (carfilzomib), as well as an anti-CD38 monoclonal antibody such as Darzalex® (daratumumab) or isatuximab; their disease is refractory to at least one of these IMiDs, at least one of these PIs, and at least one anti-CD38 monoclonal antibody; and the disease has progressed following their most recent therapy. We believe this STORM study is evaluating a cohort of patients which represents an unmet medical need, meaning there is no standard of care therapy known to be effective in this population. The STOMP study, a multi-arm clinical trial in patients with relapsed/refractory multiple myeloma, is evaluating selinexor and low-dose dexamethasone plus standard therapies, such as Revlimid®, Pomalyst®, Velcade®, Kyprolis® or Darzalex®; a new arm of the study evaluating selinexor in combination with Revlimid® in patients with previously untreated myeloma is also being opened.

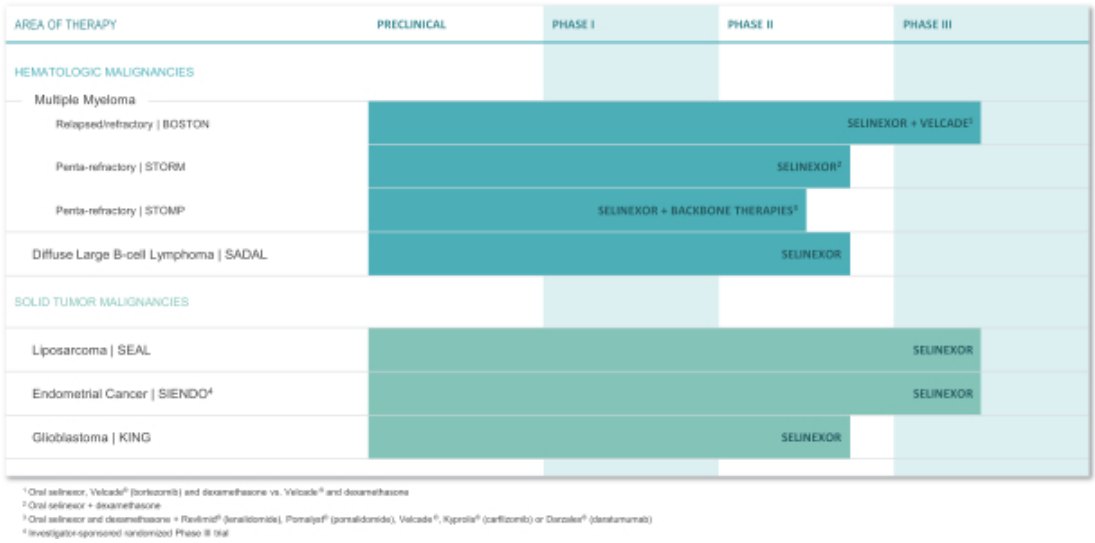
In the clinical data set for Part 1 of the STORM study, which we reported in 2016, in patients with heavily pretreated refractory multiple myeloma, selinexor demonstrated robust response rates and duration, compelling overall survival rates, and a favorable safety profile. Based on results from this Part of the STORM study, we expanded the STORM study, designated Part 2, to include approximately 120 additional patients with clearly documented penta-refractory multiple myeloma. We expect to report top-line data from Part 2 of the STORM study at the end of April 2018. Assuming a positive outcome from Part 2 of the STORM study, we plan to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) during the second half of 2018, with a request for accelerated approval for selinexor in penta-refractory multiple myeloma, followed thereafter by a potential submission to the European Medicines Agency (EMA) requesting conditional approval.

Data from the STOMP study, initially presented in December 2016 at the American Society of Hematology (ASH) annual meeting, showed that selinexor plus low-dose dexamethasone and Velcade® demonstrated high

disease response rates, including for patients whose disease was previously refractory to PIs including Velcade® and/or Kyprolis®. Based on the positive results from the Velcade® arm of the STOMP study, we are conducting the pivotal Phase 3 BOSTON study in patients with multiple myeloma who have had one to three prior lines of therapy. The BOSTON study is evaluating selinexor plus low-dose dexamethasone and Velcade® compared to low-dose dexamethasone plus Velcade®. For the BOSTON study, we have identified the combination dose of selinexor 100mg orally once weekly plus dexamethasone 20mg orally twice weekly and Velcade® 1.3mg/m^2 subcutaneously once weekly for 4 of 5 weeks, and we expect the study will enroll approximately 360 patients. If successful, the BOSTON study may qualify as a full-approval study and potentially serve as a confirmatory study if the STORM study is successful and results in accelerated and/or conditional approval.

In December 2016, we presented clinical data from the STOMP study at the ASH 2016 annual meeting indicating that selinexor and low-dose dexamethasone plus Velcade® or Pomalyst® demonstrates high response rates when combined. At the following ASH 2017 annual meeting, we presented updated clinical data from the STOMP study further indicating that selinexor and low-dose dexamethasone plus Velcade® or Pomalyst® demonstrates high response rates when combined. We also presented new data at the ASH 2017 annual meeting indicating that selinexor and low-dose dexamethasone plus Revlimid® or Darzalex® demonstrated high response rates. A year earlier at the ASH 2016 annual meeting, preliminary safety and efficacy of selinexor plus Kyprolis® (dosed twice weekly) and dexamethasone in patients with multiple myeloma was presented. The STOMP study is being expanded to evaluate selinexor plus Kyprolis® dosed once weekly. In addition, we are planning a new arm in the STOMP study that will evaluate selinexor and low-dose dexamethasone plus Revlimid® in patients with newly diagnosed multiple myeloma.

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.



[1] Oral selinexor, Velcade® (bortezomib) and dexamethasone vs. Velcade® and dexamethasone
[2] Oral selinexor + dexamethasone
[3] Oral selinexor and dexamethasone + Revlimid® (lenalidomide), Pomalyst® (pomalidomide), Velcade®, Kyprolis® (carfilzomib) or Darzalex® (daratumumab)
[4] Investigator-sponsored randomized Phase III trial

We previously announced data from the STORM, STOMP, SADAL, SEAL and KING studies and these data are described further herein. We currently expect to provide data related to the ongoing studies of selinexor listed above as follows:

STORM: Phase 2b expansion top-line data (overall response rate) in April 2018;

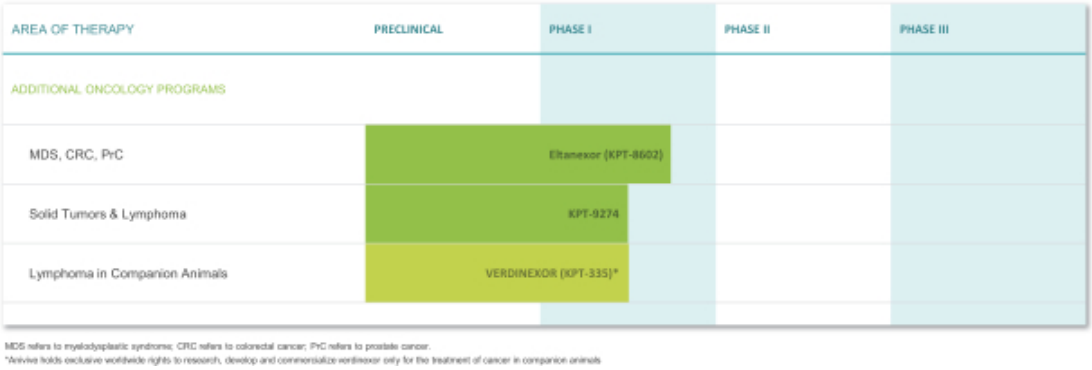
STOMP: Updated data from ongoing study arms (Revlimid®, Pomalyst®, Velcade® and Darzalex®) and potentially data from a new study arm (Kyprolis®) during 2018;

SADAL: Phase 2b top-line data (overall response rate) by the end of 2018;

BOSTON: Randomized Phase 3 top-line data (progression-free survival and overall response rate) in 2019; and

SEAL: Randomized Phase 3 top-line data (progression-free survival) by the end of 2019.

In addition to selinexor, we are also advancing a pipeline of novel drug candidates in oncology. We began clinical testing of oral eltanexor (KPT-8602), a second-generation SINE compound, in late 2015. We reported results at the ASH 2017 annual meeting showing good tolerability in patients with relapsed/refractory multiple myeloma, and we expanded clinical development of eltanexor to include myelodysplastic syndrome (MDS), colorectal cancer (CRC), and metastatic castration-resistant prostate cancer (mCRPC). We began clinical testing of oral KPT-9274, a dual PAK4/NAMPT inhibitor, in patients with lymphoma or solid tumors during 2016, and we reported top-line data at the 2017 European Society of Medical Oncology (ESMO) annual meeting showing a manageable safety profile and early signals of antitumor activity. During 2017, we licensed to Anivive Lifesciences exclusive worldwide rights for the development and commercialization of oral verdinexor (KPT-335) for the treatment of cancer in companion animals. Our pipeline of drug candidates in oncology other than selinexor is summarized in the chart below.



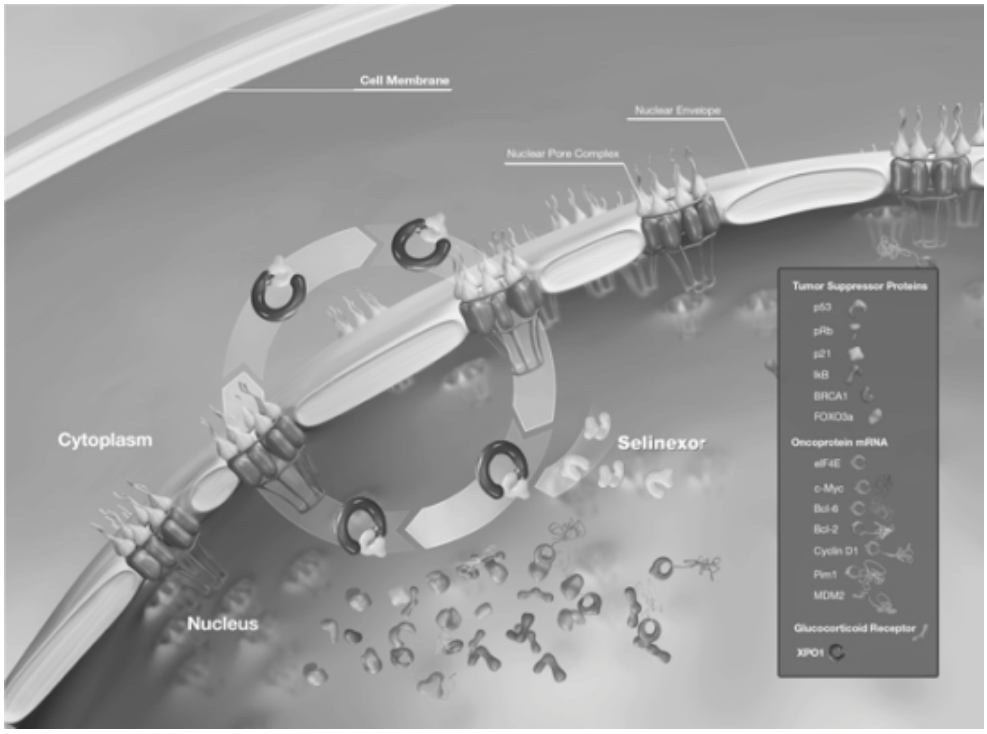
In addition to its role in cancer, XPO1 is known to play a role in neurological, inflammatory, viral, wound healing and other diseases. In the hands of academic collaborators, SINE compounds have shown activity in a variety of non-oncology models consistent with the biology of XPO1. In January 2018, we entered into an Asset Purchase Agreement with Biogen MA Inc., a subsidiary of Biogen Inc. (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 (ALS). 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.

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, and we have not generated any revenue to date from the commercial sale of any drugs. As of December 31, 2017, we had an accumulated deficit of $495.3 million. We had net losses of $129.0 million, $109.6 million and $118.2 million for the years ended December 31, 2017, 2016 and 2015, respectively. See our Consolidated Statements of Operations and Note 2 to our consolidated financial statements for further information regarding our research and development expenses and financial information regarding the geographic areas in which we operate.

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 damage and initiate programmed cell death, or apoptosis, XPO1 overexpression in cancer cells counteracts the genome surveillance process that detects DNA damage which can promote cancer. By blocking XPO1, our SINE compounds inhibit the export of tumor suppressor proteins, leading to their accumulation in the nucleus. Subsequently, the accumulation of tumor suppressor proteins amplifies their natural apoptotic function in cancer cells, but with minimal effects on normal cells. 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 the 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. Cancer treatments with our SINE compounds spare normal cells, which, unlike cancer cells, do not have significant damage to their genetic material, and we believe this selectivity for cancer cells minimizes side effects. 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 no currently approved cancer treatments and only one current clinical-stage cancer drug candidate are selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus. Thus, 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:

- ***Develop and Seek Regulatory Approval 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. 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 full or conditional approvals in other geographies as well.
- ***Maximize the Commercial Value of Selinexor.*** 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. We currently hold development, marketing, and commercialization rights for selinexor in all other countries and are positioned to develop selinexor and to seek regulatory approval for its use in oncology indications without a collaborator in North America and Europe. We are also establishing the commercial infrastructure to support a potential launch of selinexor in the United States and we intend to work with existing and potential partners to establish such commercial infrastructure outside the United States.
- ***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 top scientific advisors and physicians. We have taken this approach in the past with 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, which Biogen recently acquired from us. 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 selinexor in cancer treatment through a broad range of collaborations with leading institutions engaged in evaluating selinexor 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 (KPT-330), eltanexor (KPT-8602) and verdinexor (KPT-335) and our oral dual PAK4/NAMPT inhibitor, KPT-9274. A fifth program, KPT-350 for amyotrophic lateral sclerosis and other neuro-inflammatory conditions, was sold to Biogen in January 2018. While we may identify or in-license novel drug candidates for development in oncology in the future, we are currently focused on the development of our existing pipeline of drug candidates.

- ***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, during 2017, we licensed to Anivive Lifesciences exclusive worldwide rights for the development and commercialization of verdinexor (KPT-335) for the treatment of cancer in companion animals. 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 amyotrophic lateral sclerosis.

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 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. All large nuclear proteins (larger than 40kDa), including tumor suppressor proteins, must be transported from the cytoplasm into the nucleus to perform their functions in keeping a cell healthy. Proteins are brought into 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, 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.

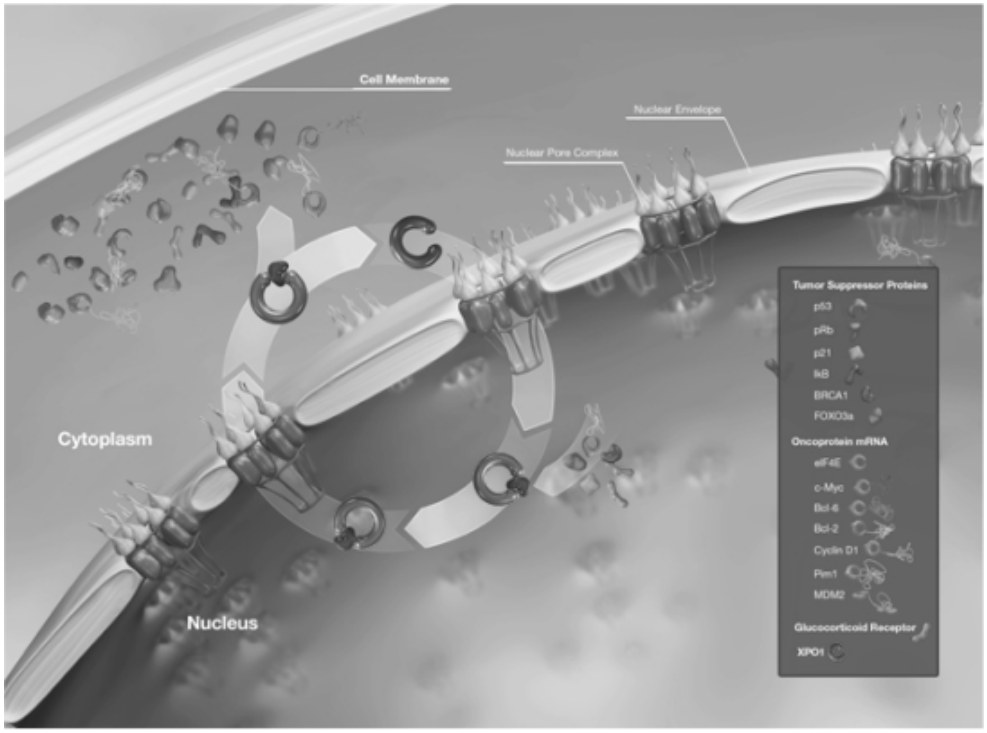
Eight exportins have been identified in human cells. One such export carrier protein was discovered in 1999 and is called exportin 1 (XPO1 or CRM1). XPO1 helps export over 220 cargo proteins. In particular, XPO1 appears to be the sole exporter for most of the tumor suppressor proteins including p53, 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 (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, Atk1, hDM2 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 protein IkB, which inhibits a protein called NF-kB. NF-kB is found in the nucleus of most cancer cells and plays a role in cancer metastasis and chemotherapy resistance, as well as in many inflammatory and autoimmune diseases. By exporting IkB out of the nucleus, XPO1 augments NF-kB 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 IkB 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-kB 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 IkB 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. Accumulation of tumor suppressor proteins increases monitoring for DNA damage and triggering of apoptosis in cancer cells. Also, blocking XPO1 can cause accumulation of 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 tumor biopsy tissues. Accumulation of IkB in the nucleus inhibits NF-kB, which may be beneficial in overcoming chemotherapy resistance and in treating autoimmune, inflammatory, and neuro-inflammatory disease. For these reasons, we believe blocking XPO1 is a good strategy for treating cancer, autoimmune, inflammatory, and neuro-inflammatory diseases. The figure below depicts the process by which XPO1 mediates the nuclear transport process.

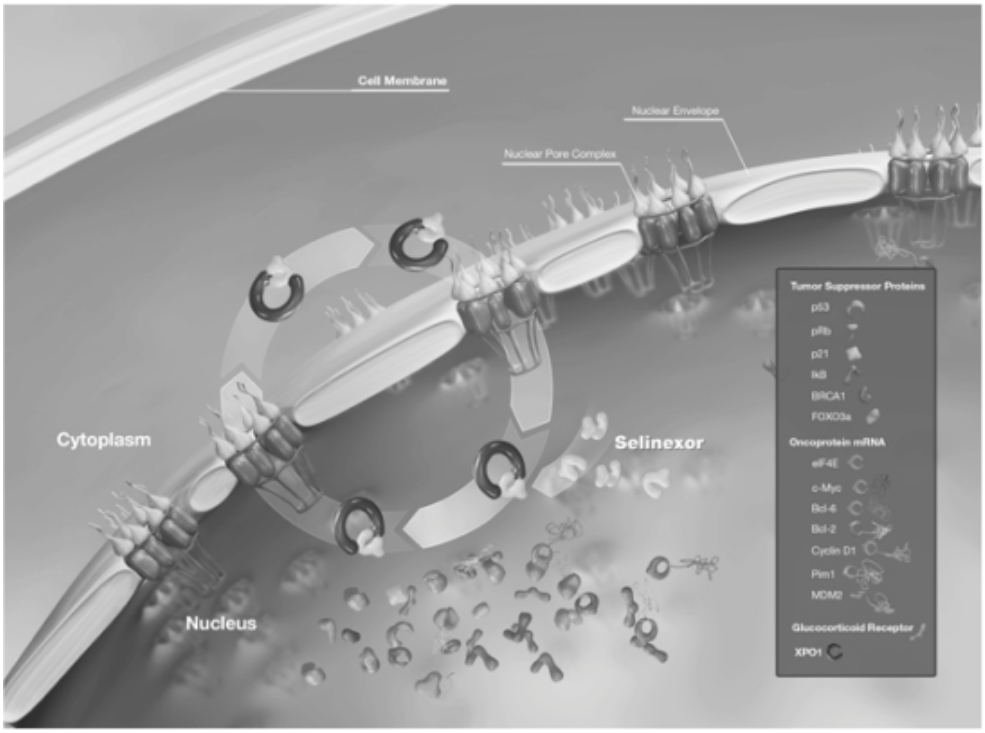
XPO1 Mediation of Nuclear Transport



Our Approach: Targeting Nuclear Export with SINE Compounds

Our lead drug candidates are first-in-class, oral, **Selective Inhibitor of Nuclear Export (SINE)** compounds. We designed SINE compounds by applying our proprietary drug discovery and optimization expertise to the X-ray structure of XPO1 published in 2009. 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 IkB 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

Cancer is the second leading cause of death globally and was responsible for 8.8 million deaths in 2015. Globally, nearly one in six deaths is due to cancer. The American Cancer Society estimates that in the United States in 2018, approximately 1.7 million new cancer cases will be diagnosed and approximately 610,000 people will die of cancer. The International Agency for Research on Cancer projects that in 2030, 21.7 million people will be diagnosed with cancer, and 13 million people will die of cancer worldwide, as compared to 14.1 million new cancer diagnoses in 2012 and 8.8 million cancer deaths worldwide in 2015.

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 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, that 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. Tumor suppressor proteins assess a cell's DNA and in cells with heavily damaged DNA, such as cancer cells, these 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.

Our Oncology Drug Candidates

Selinexor (KPT-330)

Selinexor is being evaluated in multiple later phase clinical trials in patients with relapsed and/or refractory hematological malignancies and solid tumors. Anti-cancer activity has been observed with tumor reductions and durable disease control across many hematologic malignancies and solid tumors. Over 50 patients have remained on oral selinexor, either as a single-agent or in combination with other agents, for over 12 months, with several patients on study over 24 months.

In our lead hematologic indication of relapsed or refractory multiple myeloma, selinexor has demonstrated encouraging response rates, including a 20% response rate and prolonged survival in patients whose disease is relapsed or refractory following treatment with the currently available therapies. When used in combination with other anti-myeloma agents, including Revlimid® (lenalidomide), Pomalyst® (pomalidomide), Velcade® (bortezomib) and Darzalex® (daratumumab), selinexor has generated response rates ranging from 63% to 92%. In patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), our next lead indication, selinexor has demonstrated a response rate of 33%, and similar rates in both germinal center (GCB) and non-GCB subtypes of the disease. In liposarcoma, our lead solid tumor indication, selinexor has demonstrated superior progression-free survival versus placebo, achieving a hazard ratio of 0.6, which represents a 40% reduction of disease progression or death.

To date, the most commonly reported adverse events (AEs) are predictable in the patient populations being studied and have been generally reversible and/or manageable with standard supportive care and/or dose modification. These AEs often decrease over time and are consistent with those previously reported by patients in our initial clinical trials. A preliminary analysis of safety and tolerability of selinexor was performed on unaudited AE data for 1,412 patients enrolled in our company-sponsored hematological malignancy and solid tumor clinical trials as of the data cutoff point of March 31, 2017. Overall, the most commonly reported selinexor-related AEs in ongoing clinical studies were generally low-grade and included nausea (62%), fatigue (60%), anorexia (51%), thrombocytopenia (42%), and vomiting (37%). Thrombocytopenia, the most common hematologic treatment-related AE, was reported among 42% of patients, and approximately half of these were Grades 3 to 4. The dosing regimens currently used in our key clinical trials, including BOSTON, STORM, STOMP, SADAL and SEAL, have shown predictable and manageable tolerability, particularly when used once weekly in combination regimens. In certain studies, the AEs reported from treatment arms evaluating selinexor

and dexamethasone in combination with other antimyeloma agents were similar to, or reduced, compared to selinexor and dexamethasone alone.

We describe below the key company- and investigator-sponsored studies evaluating selinexor in hematological malignancies and solid tumors, both as a single-agent and in combination. Additional data from company- and investigator-sponsored combination studies may be presented on an ongoing basis by us and/or our collaborators at scientific conferences or through other publications at various times. Unless otherwise indicated, response data presented herein are interim unaudited data based on reports by physicians at the clinical trial sites. Responses in hematological trials are measured using commonly accepted evaluation criteria for the specific indication. Responses in solid tumor trials are evaluated using RECIST unless otherwise noted.

Advanced Hematological Malignancies

Multiple Myeloma

Multiple myeloma (MM) is a hematological malignancy characterized by the accumulation of monoclonal plasma cells in the bone marrow, the presence of monoclonal immunoglobulin (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 65-70 years. In the United States, the American Cancer Society estimates that there will be approximately 31,000 new cases of MM, with about 12,800 attributable deaths, in 2018. The World Health Organization estimated that approximately 114,000 new cases of MM were diagnosed worldwide in 2012.

The treatment of MM 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® (carfilzomib), and Ninlaro® (ixazomib). Two monoclonal antibodies, Darzalex® and Empliciti™ (elotuzumab), have also recently 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 MM. 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) and cellular therapies like chimeric antigen receptor T-cell (CAR-T) therapy, nearly all patients will eventually relapse and succumb to their disease. With about 12,800 deaths from MM in the United States alone expected to occur, we believe that there remains a need for therapies for patients whose disease has relapsed after, or is refractory to, available therapy.

STORM: Phase 2b Clinical Trial of Selinexor and Low-Dose Dexamethasone in Multiple Myeloma

In May 2015, we initiated a Phase 2b clinical trial evaluating oral selinexor and low-dose dexamethasone in patients with heavily pretreated MM. The **S**elinexor **T**reatment **o**f **R**efractory **M**yeloma, or **STORM**, study is a single-arm study evaluating the treatment of relapsed/refractory MM with 80mg of selinexor and 20mg of dexamethasone, each dosed twice weekly. This 40mg per week dose of dexamethasone is considered “low dose” in the treatment of MM, compared with the “high dose” dexamethasone which uses three times more of the steroid.

At the ASH annual meeting in December 2016, we presented results, adjudicated by an independent review committee, from the first cohort of patients enrolled in the STORM study, which included patients with either quad-refractory or penta-refractory MM. Patients with quad-refractory disease had previously received prior treatments that included alkylating agents, glucocorticoids, two IMiDs (Revlimid® and Pomalyst®), and two PIs (Velcade® and Kyprolis®), and their disease is refractory to at least one IMiD and at least one PI, and has progressed following their most recent therapy. Patients with penta-refractory myeloma have quad-refractory disease that is also refractory to an anti-CD38 monoclonal antibody, such as Darzalex® or isatuximab. For the STORM study, in accordance with the FDA guidance we received, patients are required to have disease that is

refractory to Darzalex® as the anti-CD38 monoclonal antibody. We believe that this penta-refractory population represents a clear unmet medical need as this group of patients has no available or approved therapies that have demonstrated clinical benefit.

Among the 78 patients available for efficacy assessment prior to the data cutoff date of November 1, 2016, the median number of prior treatments regimens was seven and the overall response rate (ORR) as adjudicated by the Independent Review Committee (IRC) was 21% and included very good partial responses (VGPRs) and partial responses (PRs). Among the 48 patients in the quad-refractory group, the ORR was 21%. For comparison, in a similar patient population with quad-refractory disease, the anti-CD38 monoclonal antibodies Darzalex® and isatuximab had ORRs of 21% and 20%, respectively. Among the 30 patients in the penta-refractory group, the ORR was 20%. Clinical benefit rate (CBR), which is percentage of patients with a minor response (MR) or better, was 33% across all 78 patients, 29% among the patients with quad-refractory disease, and 40% among the patients with penta-refractory disease. Median overall survival (OS) was 9.3 months for all patients, longer than 11 months without a median reached in patients with a MR or better, and 5.7 months for patients who did not have any response. Median duration of response (DOR) was 5 months. Cytopenias of Grade 3 or Grade 4 were the most common side effects and were generally not associated with clinical sequellae. Nausea, anorexia and fatigue were the most common non-hematological side effects, primarily Grades 1 and 2, and were treatable with supportive care and/or dose modification. There were low rates of non-hematologic toxicities of Grades 3 or 4, with no new safety signals identified. In particular, there was one reported case of Grade 4 infection (1.3%), one reported case of Grade 2 neuropathy (1.3%) and one reported case of sepsis (1.3%).

Based on these results, we expanded the STORM study to add an additional cohort of approximately 122 additional patients with penta-refractory MM. The primary endpoint of the STORM study is ORR as adjudicated by the IRC. The trial has several secondary endpoints including the median DOR.

We expect to report top-line data from the expanded STORM cohort at the end of April 2018. Assuming a positive outcome from the expanded cohort of the STORM study, we plan to submit an NDA to the FDA during the second half of 2018 with a request for accelerated approval for selinexor in penta-refractory MM, followed thereafter by a potential submission to the EMA requesting conditional approval in this same patient population.

STOMP: Phase 1b/2 Clinical Trial of Selinexor in Combination with Backbone Therapies in Multiple Myeloma

Based on preclinical synergy in animal models of MM, in October 2015, we initiated a Phase 1b/2 clinical study of oral selinexor in combination with available treatments for relapsed/refractory MM. In this multi-arm study, **Selinexor and Backbone Treatments of Multiple Myeloma Patients** (**STOMP)**, we are evaluating the combination of selinexor and low-dose dexamethasone with Revlimid®, Pomalyst®, Velcade®, Kyprolis® and Darzalex® in patients with previously treated MM. Each combination is evaluated on a separate arm of the STOMP study and within each combination, two treatment cohorts evaluate once weekly versus twice weekly dosing of selinexor. The primary objectives of the Phase 1 portion are to determine the maximum tolerated dose and recommended Phase 2 and Phase 3 doses for selinexor in these combination therapies. The primary objectives of the Phase 2 portion are to assess preliminary efficacy through ORR, CBR and DOR.

Selinexor in Combination with Velcade® and Low-dose Dexamethasone (SVd)

At the ASH 2017 annual meeting, we presented updated results from the selinexor, Velcade® and dexamethasone arm of the STOMP study, referred to as SVd, at the 2017 ASH annual meeting. In this study arm, oral selinexor was dose-escalated in once-weekly (80 or 100mg) or twice-weekly (60 or 80mg) regimens. Velcade® (1.3mg/m2 subcutaneously) was administered once-weekly or twice-weekly. Dexamethasone was administered orally either 40mg once-weekly or 20mg twice-weekly. The patients in this cohort were heavily pretreated and many (43%) had MM refractory to a proteasome inhibitor. Across the 42 patients enrolled in the SVd arm as of November 15, 2017, the median number of treatment regimens was three (range of one to 11 prior

treatment regimens). Of the overall 40 patients evaluable for efficacy, as of November 15, 2017, 25 responded for an ORR of 63% (three patients having a complete response, or CR, nine patients having a VGPR and 13 patients having a PR). The majority of patients had reductions in M-protein, including 33% with a 90% or greater reduction. Among the 19 patients with PI relapsed/naïve disease, the ORR was 84% and the median progression-free survival (PFS), was greater than 13 months. The results were similar in the subgroup of 18 patients with PI relapsed/naïve disease and between one and three prior treatment regimens, which is also the patient population closest to those eligible for the BOSTON study. These response rates compare favorably to standard Vd regimens (the control arm of the BOSTON study), which typically show response rates of 60% to 65% and PFS of seven to nine months across many previous studies. Amongst the 21 patients with PI-refractory disease where retreatment with Vd alone would not be expected to induce a significant response, the ORR following SVd treatment was 43%, suggesting that the addition of selinexor to Vd in patients with PI-refractory MM could resensitize their disease to a treatment regimen including a PI.

Based on these data, the recommended dose regimen for the SVd arm was identified as selinexor (100mg once weekly), Velcade® (1.3mg/m^2 weekly given sub-cutaneously for four of five weeks) and dexamethasone (40mg weekly), which represents 40% less Velcade® and 25% less dexamethasone compared to the approved standard Vd regimen. Among the 42 patients evaluable for safety as of the November 15, 2017 data cutoff date, the most common Grade 1/2 AEs were nausea (57%), anorexia (57%), fatigue (45%), diarrhea (36%) and vomiting (29%). Importantly, the reported peripheral neuropathy across all patients was Grade 1/2 and limited to six patients (14%), of which five had prior Velcade® exposure. The most common Grade 3 or higher AEs were thrombocytopenia (45%), neutropenia (24%), fatigue (14%) and anemia (12%).

Selinexor in Combination with Pomalyst® and Low-dose Dexamethasone (SPd)

At the ASH 2017 annual meeting, we also presented updated results from the selinexor, Pomalyst® and dexamethasone arm of the STOMP study, referred to as SPd. In this study arm, selinexor was dosed orally either once weekly (60 or 80mg) or twice weekly (60 or 80mg) with Pomalyst® (4mg orally, once daily) and dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the 31 patients enrolled in the SPd arm as of November 1, 2017, the median number of prior treatment regimens was four (range of two to nine prior treatment regimens). Of the overall 27 patients evaluable for efficacy as of November 15, 2017, 15 responded for an ORR of 56% (two patients having a VGPR and 13 patients having a PR). In the Pomalyst®-naïve and Revlimid®-relapsed or -refractory population (19 patients), the ORR was 63% and the median PFS was 11.6 months. Responses tended to occur rapidly with a median of one month to onset. The median PFS of 11.6 months for SPd compares favorably with the PFS of approximately 4 months reported for standard Pd regimens in the Revlimid®-refractory or -relapsed population.

Among the 31 patients evaluable for safety as of November 1, 2017, the most common Grade 1/2 AEs were nausea (52%), anorexia (45%), fatigue (45%) and diarrhea (32%). The most common Grade 3 or higher AEs were neutropenia (55%), thrombocytopenia (32%) and anemia (29%). Gastrointestinal AEs were generally manageable with antiemetics. There were two Grade 5 treatment-related events (febrile neutropenia and intracranial hemorrhage). Five dose limiting toxicities (DLTs) (Grade 3 fatigue, neutropenia and febrile neutropenia) were observed in patients receiving selinexor 60mg twice weekly or 80mg once weekly. Based on the activity and tolerability observed in this study arm, doses of oral selinexor of 60mg and 80mg once weekly are being evaluated in combination with Pomalyst® (3mg orally, once daily) and low dose dexamethasone to determine the recommended Phase 2 dose for this combination regimen.

Selinexor in Combination with Revlimid® and Low-dose Dexamethasone (SRd)

At the ASH 2017 annual meeting, we also presented new data from the selinexor, Revlimid® and dexamethasone arm of the STOMP study, referred to as SRd. In this study arm, oral selinexor was dose-escalated starting at either 60mg once weekly or 60mg twice weekly, with Revlimid® (25mg orally, once daily), and dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the 19 patients enrolled in the SRd

arm as of November 1, 2017, the median number of prior treatment regimens was one (range of one to seven prior treatment regimens). Of the 16 patients evaluable for efficacy, as of November 15, 2017, 13 responded for an ORR of 81% (three patients having a VGPR and 10 patients having a PR). Among the 12 patients in the Revlimid®-naïve population, the ORR was 92%. Median PFS was not reached for either the overall study population or for patients with Revlimid®-naïve disease. The median time on treatment for the overall study population was also not reached.

Among the 19 patients evaluable for safety as of November 15, 2017, the most common Grade 1/2 AEs were nausea (68%), anorexia (42%), fatigue (42%), weight loss (42%), constipation (32%) and vomiting (32%). The most common Grade 3 or higher AEs were thrombocytopenia (68%) and neutropenia (58%). Gastrointestinal AEs were generally manageable with antiemetics. Five DLTs (thrombocytopenia (four patients) and anorexia (one patient)) were observed in patients receiving selinexor 60mg twice weekly and 80mg once weekly. Thrombocytopenia and anorexia were reduced in the selinexor 60mg once weekly cohort versus the twice weekly groups. Based on the activity and tolerability observed in this study arm, the recommended dose of the all-oral SRd is selinexor (60mg orally, once weekly), Revlimid® (25mg orally, once daily) and dexamethasone (40mg orally, once weekly).

Selinexor in Combination with Darzalex® and Low-dose Dexamethasone (SDd)

At the ASH 2017 annual meeting, we presented new data from the selinexor, Darzalex® and dexamethasone arm of the STOMP study, referred to as SDd. In this study arm, oral selinexor was dose escalated using either 100mg once weekly or 60mg twice weekly, with Darzalex® (16mg/kg intravenously once weekly) and dexamethasone (orally, 40mg once weekly or 20mg twice weekly). Across the nine patients enrolled in the SDd arm as of November 1, 2017, the median number of prior treatment regimens was four (range of two to 10 prior treatment regimens). Of the eight patients evaluable for efficacy, as of November 15, 2017, five responded for an ORR of 63% (three patients having a VGPR and two patients having a PR). Among the six patients in the Darzalex®-naïve population, the ORR was 83%. Responses tended to occur rapidly with a median of one month to onset.

Among the nine patients evaluable for safety as of November 15, 2017, the most common Grade 1/2 AEs were fatigue (44%), nausea (33%) and neutropenia (33%). The most common Grade 3/4 AEs were thrombocytopenia (56%), leukopenia (44%), anemia (44%) and neutropenia (33%). Gastrointestinal AEs were generally manageable with antiemetics. The maximum tolerated dose was not reached. Two DLTs (Grade 3 thrombocytopenia and Grade 2 fatigue) were observed in patients receiving selinexor 60mg twice weekly; both patients showed responses. Based on the preliminary tolerability and efficacy data, the RP2D of SDd is selinexor (100mg orally, once weekly), Darzalex® (16mg/kg, once weekly) and dexamethasone (40mg orally, once weekly).

Selinexor in Combination with Kyprolis® and Low-dose Dexamethasone (SKd)

We are conducting an additional arm of the STOMP study evaluating selinexor, Kyprolis® and dexamethasone, referred to as SKd. Based on investigator-sponsored trial data reported in 2016 with this combination, the dosing regimen selected for STOMP is selinexor (100mg once weekly), Kyprolis® (56 or 70mg/m^2 intravenously once weekly) and dexamethasone (40mg orally, once weekly). We expect to report preliminary results from the SKd arm by the end of 2018.

Selinexor in Combination with Revlimid® and Low-dose Dexamethasone in Newly Diagnosed Multiple Myeloma (SRd NDMM)

We plan to conduct an additional arm of the STOMP study evaluating selinexor, Revlimid® and dexamethasone in patients with newly diagnosed multiple myeloma (NDMM), referred to as SRd NDMM. Patients eligible for this arm must have symptomatic NDMM requiring systemic therapy. Eligible patients must

not have had any prior systemic therapy for NDMM other than corticosteroids. We expect that starting dose of oral selinexor will be 60mg (once weekly) with 40mg of dexamethasone (orally, weekly) and 25mg of Revlimid® (orally, once daily).

BOSTON: Pivotal Phase 3 Clinical Trial of Selinexor, Velcade® and Low-Dose Dexamethasone vs. Velcade® and Low-Dose Dexamethasone in Multiple Myeloma

Based on the data from the SVd arm of the STOMP study and following consultation with the FDA and the EMA, we are conducting a pivotal randomized Phase 3 study, known as the BOSTON (**Bortezomib, Selinexor and dexamethasone**) study, which is evaluating SVd compared to standard Velcade® and low-dose dexamethasone (Vd) in patients with MM who have had one to three prior lines of therapy. We expect that the BOSTON study will enroll approximately 360 patients who will be randomized in a one-to-one fashion to receive either SVd or Vd. The dosing schedule allows for only one scheduled clinic visit per week for patients on the SVd arm with selinexor and Velcade® to be dosed not more frequently than once per week. Importantly, dosing on the SVd arm will use 40% less Velcade® and 25% less dexamethasone than the Vd arm, which will follow the standard Vd dosing schedule. We expect that the reduced exposure provided by the SVd dosing schedule may significantly reduce common Velcade®- and dexamethasone-related toxicities, which is consistent with the safety data from the 42 patients described above who were treated with SVd on the STOMP study at the recommended dose. For the Vd arm, cross-over to the SVd arm based on objective progression will be permitted. The primary endpoints of the study are ORR and PFS and key secondary endpoints include DOR, OS, and certain other duration and quality of life endpoints. Top-line data from the Phase 3 BOSTON study is anticipated in 2019.

Non-Hodgkin's Lymphoma

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. DLBCL is the most common and the most aggressive of the different forms of NHL. We estimate that approximately 25,000 patients are diagnosed with DLBCL in the United States each year, with approximately 10,000 deaths per year. 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 overall survival 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 be medically stable enough to undergo CAR-T therapy and have no new or targeted agents approved for the treatment of their disease.

SADAL: Phase 2b Clinical Trial of Selinexor in Diffuse Large B-Cell Lymphoma

Our **Selinexor Against Diffuse Aggressive Lymphoma**, or **SADAL**, study is an open-label Phase 2b clinical trial evaluating single-agent oral selinexor in patients that have relapsed and/or refractory DLBCL, either de novo or transformed from a more indolent NHL such as follicular lymphoma, after two to five lines of therapy. At least 50% of patients on SADAL will have the GCB subtype of DLBCL, which represents a particularly high unmet medical need given the lack of available therapies for patients with this relapsed/refractory subtype. The SADAL study had been conducted as a two-arm study with patients randomized on a one-to-one basis to receive either 100mg or 60mg of selinexor, each given twice weekly, with about 200 patients expected to be randomized evenly between the two arms with an inclusion requirement of least 14 weeks since a patient's last systemic anti-DLBCL therapy. The primary endpoint would be ORR on each arm, with the goal of determining the more optimal dose for patients with heavily pretreated DLBCL.

In early 2017, we reported efficacy data to the FDA across both the 100mg and 60mg arms in the first 63 patients with consistent response rates across both arms (adjudicated by independent central radiological

committee per protocol), but greater durability and chronic tolerability were observed in the 60mg arm. The FDA agreed that the change to a single-arm study was reasonable and that the proposed trial design and indication appeared appropriate for accelerated approval, though the availability of accelerated approval will depend on the trial results and available therapies at the time of regulatory action. Therefore, in consultation with the FDA, we amended the SADAL study to become a single-arm study evaluating single-agent selinexor at 60mg given twice weekly and to make other protocol amendments, including to reduce the 14-week washout period to 60 days in patients who achieved at least a PR on their most recent therapy; patients with stable disease (SD) on their most recent therapy still require the 14-week washout period.

In June 2017, we reported updated results from the SADAL study at the 2017 European Hematology Association (EHA) annual meeting. Across the 90 patients enrolled in SADAL as of May 15, 2017, the median number of prior treatment regimens was three (range of two to five prior treatment regimens). Based on the intention-to-treat analysis of the first 63 patients and as adjudicated by an independent central radiological review committee, as of May 15, 2017, 21 patients responded (nine patients having a CR and 12 patients with a PR) for an ORR of 33%. An additional six patients experienced SD, for a disease control rate (DCR) of 43%. The median DOR across all patients was greater than seven months and responses tended to occur rapidly with a median of two months to onset. Among patients who responded, the median time on treatment was nine months with a follow up of 12.8 months. Nine patients who responded remained on treatment as of the data cutoff date, including six patients with a CR. The median overall survival was eight months for all patients on the study. Median survival for the patients with PR or CR had not been reached and is over nine months. Consistent with published survival data in this population and a lack of effective alternative therapeutic options, the median survival for patients with SD, PD or non-evaluable was 4.8 months.

Selinexor also demonstrated robust, single-agent activity against both GCB and non-GCB subtypes of DLBCL. Of the 32 patients with DLBCL of the GCB-subtype, nine responded (four patients having a CR, five patients having a PR) for an ORR of 28%. Of the 31 patients with DLBCL of the non-GCB (or ABC)-subtype, 12 responded (five patients with a CR, seven patients with a PR) for an ORR of 39%.

Among the 90 patients evaluated for safety, the most common AEs across both dosing groups were fatigue (61%), nausea (51%), thrombocytopenia (50%), anorexia (49%), vomiting (31%) and anemia (30%), and were primarily Grades 1 and 2 and were managed with dose modifications and/or standard supportive care. As expected, the most common Grade 3 and 4 AEs in the 60mg arm were thrombocytopenia (28%), neutropenia (17%), anemia (15%), and fatigue (11%) and were manageable with dose modifications and/or standard supportive care.

The SADAL study is expected to enroll a total of approximately 130 patients at the 60 mg twice weekly dose, and we anticipate announcing top-line data for the completed study by the end of 2018. Additional studies of selinexor in combination with standard DLBCL treatments are ongoing or are being planned, and we anticipate that one or more of these studies will inform the design of a randomized phase 3 study to be initiated in the future.

Investigator-Sponsored Trials

Ongoing investigator-sponsored clinical trials are evaluating the safety and efficacy of selinexor in combination with existing therapies to treat various lymphomas: (i) rituximab, ifosfamide, carboplatin and etoposide, or R-ICE, and selinexor to treat relapsed (at least one prior therapy) DLBCL and other aggressive lymphomas, (ii) ibrutinib and selinexor to treat chronic lymphocytic leukemia or NHL, and (iii) R-DHaOx and R-GDP in combination with selinexor in relapsed refractory B-cell lymphomas including DLBCL.

Acute Myeloid Leukemia

AML in elderly populations remains a vexing clinical problem with limited progress in the last decade. There are limited treatment agents approved for patients that are ineligible for standard intensive chemotherapy.

AML is a cancer that starts in the bone marrow and in most cases quickly moves into the blood. The incidence of AML dramatically increases after the age of 55. The American Cancer Society estimates that approximately 19,500 new cases of AML, most of which will be in adults, will be diagnosed in the United States in 2018, with approximately 10,600 deaths from AML in the United States in 2018. Approximately 40% of AML patients are young enough with sufficient major organ function to undergo stem cell transplantation for their AML, and approximately 50% of these patients can be cured of their disease. Therefore, approximately 20% of adults with AML are currently curable. Those who are not cured, and those patients who are elderly or unfit for transplant, have a very poor prognosis with a median survival of less than one year. Recently, selective inhibitors of isocitrate dehydrogenase (IDH1 or 2) proteins have been developed for the approximately 20% of patients whose AML harbors these mutations, and a liposomal fixed-dose formulation of standard chemotherapy agents for patients with secondary AML have been developed and/or approved. However, for the majority of patients with AML, there remains no effective treatment. Moreover, prognosis worsens continuously with advancing age to a median survival of as low as one month for those who are older than 85 years of age.

SOPRA: Phase 2 Clinical Trial of Selinexor vs. Physician's Choice in Elderly AML

Our Phase 2 study of oral selinexor in patients 60 years of age or older with relapsed or refractory AML enrolled patients who were ineligible for standard intensive chemotherapy and/or transplantation. In our **Selinexor in Older Patient with Relapsed/ Refractory AML** (**SOPRA**) study, we enrolled 176 patients who have AML that has relapsed after, or was refractory to, first line therapy. Patients were randomized in a 2:1 fashion to selinexor provided orally twice weekly in a dose of 60mg plus best supportive care (BSC) versus one of three physician choices (PC). SOPRA enrolled 176 patients, with a median of two prior treatment regimens. In March 2017, we reported that we had determined, in concert with SOPRA's independent Data Safety Monitoring Board (DSMB), that the study would not reach statistical significance for showing superiority of OS on selinexor versus OS on PC, the study's primary endpoint. Based on unaudited site data, among patients on the selinexor arm, 13% demonstrated a CR with or without full hematologic recovery (CRi), compared to 3% of patients on the PC control arm. Some patients remained on selinexor for over one year, but this did not result in a statistically superior OS compared to the PC arm. However, since the 13% of selinexor-treated patients who achieved a CR (with or without full hematologic recovery) showed a substantial OS benefit as compared with the PC arm, we and the DSMB agreed that patients would be permitted to continue on the selinexor arm or the PC arm, as applicable, following discussion between the patient and their treating physician.

The DSMB found no new clinically significant AEs in the patients receiving selinexor. Rates of sepsis and febrile neutropenia (FN) were lower on the selinexor arm than the PC arm: on selinexor, the rate of sepsis was 4.9% versus 6.1% for the PC arm; the rate of FN on selinexor was 14.7% versus 36.4% on the PC arm. As expected, the most common selinexor-related AEs were nausea, anorexia, fatigue, vomiting, and thrombocytopenia.

We plan to continue clinical development of selinexor in AML through investigator-sponsored trials in multiple combination regimens, including with chemotherapy, given data to date across these settings.

Investigator-Sponsored Trials

SAIL: Phase 2 Clinical Trial of Selinexor, Ara-C and Idarubicin in AML

In December 2016, Walter Fiedler, MD of the University Medical Center Hamburg-Eppendorf in Germany and his colleagues presented updated data from the SAIL study, an investigator-sponsored trial evaluating the combination of selinexor, Ara-C and idarubicin in patients with relapsed/refractory AML. Patients in this study had a range of one to five prior therapies and 39% had undergone a prior stem cell transplant or donor lymphocyte infusion. Data from 42 patients evaluable for safety (range of prior treatment regimens, all including intensive chemotherapy is 1-5), as of October 2016, demonstrated an ORR of 55% (with 4 patients excluded from evaluation due to early death) and included CR of 22% and 36% and CRi of 33% and 9% in Cohort 1 and 2, respectively. Median relapse free survival was 333 days and median OS was 435 days.

The most frequent Grade 3 or higher non-hematologic AEs of this intensive chemotherapy-containing regimen were diarrhea (50%) and nausea (12%). The most common Grade 3 or higher hematologic AEs were neutropenia (100%) and thrombocytopenia (100%) as expected with any intensive chemotherapy regimen. Two deaths occurred that were deemed possibly treatment-related, which were one reported case of systemic inflammatory response syndrome (SIRS; 2%) and one reported case of hemophagocytosis syndrome (2%). Other Ara-C-based combination therapies for AML have shown significantly lower response rates in patients with heavily pretreated AML: combination of Ara-C with Mylotarg® (gemtuzumab ozogamicin) – 11.5% ORR; combination of Ara-C with doxorubicin (Doxil®) – 6.9%. We believe the combination of selinexor with chemotherapy is a promising regimen, particularly in this difficult-to-treat patient population with poor prognoses. Approximately half of patients on the SAIL study were able to proceed to their first or second allogeneic stem cell translation. Ara-C and idarubicin represent the standard of care for AML patients who are candidates for intensive therapy, and the SAIL study provides support for the tolerability of selinexor in combination with standard of care therapy. Accordingly, we believe that selinexor in combination with Ara-C and idarubicin may be an effective treatment option and serve as a bridge to stem cell transplantation for patients with relapsed/refractory AML.

Additional investigator-sponsored studies are evaluating the safety and efficacy of selinexor as a single agent and in combination with existing therapies: (i) daunorubicin, cytarabine and selinexor in patients with high risk, naïve AML, (ii) topoisomerase-II inhibition and selinexor in AML, (iii) sorafenib and selinexor in AML, (iv) cladribine and cytarabine, or CLAG, and selinexor in AML, (v) high dose cytarabine, or HiDAC, mitoxantrone chemotherapy and selinexor for remission induction in AML, (vi) decitabine and selinexor in AML, (vii) fludarabine, cytarabine and selinexor in pediatric patients with relapsed/refractory leukemia or MDS, (viii) single-agent selinexor to eliminate minimal residual disease and maintain remission in patients with AML and high risk MDS after allogenic stem cell transplant and (ix) single-agent selinexor in MDS.

Eighteen pediatric patients with relapsed or refractory leukemia were enrolled in the investigator-sponsored SELHEM (Selinexor with Fludarabine and Cytarabine for Treatment of Refractory or Relapsed Leukemia or Myelodysplastic Syndrome) clinical trial. Data from this study were presented in May 2016 at the American Society of Pediatric Hematology/Oncology Annual Meeting and published in August 2016 in the Journal of Clinical Oncology. In the SELHEM study, selinexor was given orally six times per 28-day cycle. Among the 17 patients who were evaluable for toxicity, three were treated with selinexor at 30mg/m^2, three at 40mg/m^2, six at 55mg/m^2, and five at 70mg/m^2. Fludarabine (30mg/m^2) and cytarabine (2g/m^2) were each administered twice during each 28-day cycle.

In this group of heavily pretreated, relapsed and/or refractory patients, seven of 15 evaluable patients (47%) achieved CR or CRi. Five of the responses were negative for minimal residual disease, or MRD. Two patients experienced MRD negative CRs within the first cycle after receiving only oral selinexor therapy. The most common Grade 3 nonhematologic toxicity was asymptomatic hyponatremia. Two patients who were treated with selinexor at 70mg/m^2 experienced reversible cerebellar toxicity, thereby defining the dose-limiting toxicity. The SELHEM study concluded that selinexor, in combination with fludarabine and cytarabine, is tolerable at doses up to 55mg/m^2 in pediatric patients with relapsed or refractory leukemia. Given the promising response rates, further exploration of this combination is expected in a Phase 2 clinical trial.

Advanced or Metastatic Solid Tumor Malignancies

Solid tumors represent the vast majority of cancer incidences. Given the large patient population with solid tumors and the mechanistic activity of selinexor that makes it potentially suitable for treating any type of cancer, we are developing selinexor to potentially play a meaningful role across multiple solid tumor indications, either alone or in combination as a backbone therapy. We have seen encouraging single agent data for selinexor in a variety of solid tumors including PRs and durable 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 (GBM) also

demonstrated anti-cancer activity and disease control. Given the promising single-agent activity in difficult-to-treat indications and the potential to enhance activity in combination with existing therapies, we plan to evaluate opportunities to develop selinexor in unmet needs like certain gynecological malignancies or GBM, and to advance combination therapy development with both standard of care and emerging therapies like immune checkpoint inhibitors.

SEAL: Phase 2/3 Clinical Trial of Selinexor vs. Placebo in Liposarcoma

Liposarcoma represents an area of high unmet need with limited treatment options. 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 Sates. 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.

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. Of the 18 patients with liposarcoma, 14 (78%) experienced SD and eight (44%) experienced SD of four months or longer. Fifteen of these 18 patients with liposarcoma 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 **Selinexor in Advanced Liposarcoma** (**SEAL**) 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 given twice weekly until progression or intolerability. In September 2017, we reported a successful outcome from the Phase 2 portion of the SEAL study (57 patients). For the study's primary endpoint of PFS, selinexor showed superiority over placebo, achieving a hazard ratio (HR) of 0.6, representing a 40% reduction in the risk of progression or death. PFS was assessed by an Independent Central Radiological Review (ICRR) based on RECIST v1.1. In this randomized, blinded Phase 2 portion of the study, selinexor demonstrated an expected and manageable safety profile, primarily with nausea, anorexia and fatigue 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 standard supportive care. Importantly, the incidence of infections in the selinexor arm (overall 29%; Grade 3 or higher, 0%) was less than that reported in the placebo arm (overall 39%; Grade 3 or higher, 19%). Additional efficacy assessments included PFS by World Health Organization (WHO) response criteria, effects on metabolic parameters via PET Scans, and PFS according to Choi Criteria. PFS per WHO criteria achieved a HR of 0.84; the WHO response criteria will not be included as part of the Phase 3 study objectives.

The Phase 3 portion of the SEAL study, which was originally initiated in North America, is ongoing and has been expanded to include Europe. In this blinded, placebo-controlled Phase 3 study, up to 222 patients are expected to be enrolled and 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 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 by the end of 2019. Assuming a positive outcome, these data are intended to support a NDA for oral selinexor as a potential new treatment for patients with advanced unresectable dedifferentiated liposarcoma.

*SIENDO: Investigator-Sponsored Randomized Phase 3 Trial of Maintenance **S**elinexor/Placebo After Combination Chemotherapy **I**n Patients with Advanced or Recurrent **ENDO**metrial Cancer*

SIENDO is an investigator-sponsored Phase 3 trial of maintenance with selinexor or placebo after combination chemotherapy for patients with advanced or recurrent endometrial cancer. The overall objective is to obtain conclusive evidence of efficacy for maintenance selinexor in patients with advanced or recurrent endometrial cancer. This is a multi-center/multinational trial expected to enroll 160 patients.

This investigator-sponsored 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 October 2016, we presented updated data at the 2016 ESMO annual meeting that showed selinexor's promising anti-tumor activity and disease control in gynecological malignancies. Of the 59 evaluable patients with ovarian cancer, 29 met the primary endpoint (8 patients (14%) achieved a confirmed PR and 21 patients achieved SD for at least 12 weeks), for a DCR of 49%. Median PFS for the ovarian cancer arm was three months and median OS was seven months. Of the 20 evaluable patients with endometrial cancer, nine met the primary endpoint (three confirmed PRs and six with SD for 12 or more weeks), for a DCR of 45%. Median PFS for the endometrial cancer arm was three months and median OS was eight months. Across all arms, the most common Grade 2 or 3 AEs were fatigue, nausea, anemia, anorexia, vomiting, weight loss and thrombocytopenia, which were manageable with supportive care and dose modifications. Notably, Grade 3 AEs were significantly reduced in patients with ovarian cancer receiving once weekly dosing compared to twice weekly dosing. One incidence of Grade 4 thrombocytopenia without bleeding was also reported. For the 44 patients achieved at least SD for at least 12 weeks, the median time on study was 20 weeks. Fifteen patients remained on single-agent selinexor for greater than 6 months, including 4 patients continuing on treatment for greater than 12 months.

KING: Phase 2 Clinical Trial of Selinexor 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 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/m^2 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.

Investigator-Sponsored Trials

Investigator-sponsored clinical trials are evaluating the safety and efficacy of selinexor as a single agent and in combination with existing therapies: (i) selinexor, paclitaxel and carboplatin in ovarian or endometrial malignancies, (ii) selinexor and standard chemotherapy agents in advanced solid tumors, (iii) selinexor in genomic profiling and matched therapy for recurrent or metastatic salivary gland neoplasms, (iv) selinexor in Asian patients with advanced malignancies and (v) selinexor in recurrent refractory pediatric solid tumors.

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.

Eltanexor differs from selinexor primarily because it has much lower penetration into the brain and, therefore, may cause fewer side effects such as nausea, fatigue and anorexia. 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. In many preclinical model systems, the more intensive dosing regimen leads to superior efficacy in comparison to selinexor treatment. 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 2017 ASH annual meeting, we reported positive data from the ongoing Phase 1/2 study demonstrating good tolerability and promising activity in MM. Using a 3+3 dose escalation design, oral eltanexor (5, 10, 20, 30 and 40mg) was dosed once daily for five days per week or once every other day for three days each week (60mg) for a 28-day cycle. Patients with less than a minimal response after one cycle or partial response after two cycles were permitted to add dexamethasone. Of the 34 evaluable patients, 14 received dexamethasone with their eltanexor regimen from the first day of the first cycle. Objective responses correlated with longer overall survival and all patients with a VGPR or PR were still alive or censored as of the data cutoff date. Deeper and faster responses were observed when dexamethasone was started on Day 1 of Cycle 1 versus a delayed start. Among the 35 patients evaluable for M-protein, 25 patients (71%) had reductions in M-protein. The median time on treatment for the overall study population was greater than 96 days, with a range of 10 to 441 days.

Among the 39 patients evaluable for safety, the most common Grade 1/2 AEs 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, 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 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, advanced CRC or mCRPC. 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. We believe eltanexor has the potential to control malignancies in these indications with a favorable side effect profile.

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 (PAK4) and NAMPT (nicotinamide phosphoribosyltransferase; also known 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.

PAK4 is a signaling protein regulating numerous fundamental cellular processes, including several involved in the development of cancer. PAK4 interacts with key signaling molecules involved in cancer such as beta-catenin, CDC42, Raf-1, BAD and myosin light chain.

NAMPT is a pleiotropic protein with multiple intra- and extra-cellular functions that can be found in complex with PAK4 in the cell. NAMPT is of interest as an oncology target because it catalyzes the rate-limiting step in one of the two intracellular salvage pathways that generate nicotinamide adenine dinucleotide (NAD). NAD is a universal energy- and signal-carrying molecule involved in mitochondrial function and energy

metabolism, as well as in DNA repair (through Poly-ADP-Ribose Polymerase, or PARP) and epigenetics (through sirtuims, or SIRTs). An alternate salvage pathway utilizes the rate-limiting enzyme NAPRT1 to convert nicotinic acid or niacin into NAD. NAPRT1 is often silenced through promoter hypermethylation in tumor samples while it remains expressed in normal tissues. Patients that have NAPRT1 negative tumors may be able to benefit from niacin co-dosing to alleviate KPT-9274 adverse effects while maintaining inhibitory activity in their tumors. Therefore, patients can be stratified according to their NAPRT1 tumor status.

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 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 (shrinkage of 3.9%, 13.6% and 22.6%) were observed in three out of three patients (100%) 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 (NAPRT1- : 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.

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. We have received a Minor Use / Minor Species (MUMS) designation from the FDA's Center for Veterinary Medicine (CVM) for the treatment of newly-diagnosed or first relapse after chemotherapy lymphomas in pet dogs with verdinexor.

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. In this Phase 2b clinical trial, Verdinexor was administered initially at doses ranging from 25mg/m^2 to 30mg/m^2 two or three days per week. Minimal or no supportive care was given. The total CRs and PRs of the 58 dogs was 34%, with one CR and 19 PRs. An additional 33 of 58 dogs (57%) experienced SD for at least four weeks. The median time to disease progression

was approximately five weeks, with 20 dogs (34%) remaining on study for longer than eight weeks. A few dogs that received verdinexor in the Phase 1 or 2b studies remained on therapy for longer than eight months. 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 (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 oral, targeted therapy for the treatment of dog lymphoma.

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, rare disease and autoimmune indications, in addition to the canine lymphoma program described above. 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 Respiratory Syncytial Virus and Epstein Barr Virus.

In addition to viral indications, we plan to study verdinexor in preclinical models of various rare diseases such as Rett syndrome, Leishmania and Trypanosoma. We believe the anti-inflammatory and neuroprotective properties of SINE compounds could benefit patients in these difficult to treat rare diseases. We also plan to study verdinexor in autoimmune indications. We believe autoimmune diseases are a rational target for verdinexor as elevated XPO1 function appears to contribute to disease pathology in indications with dysregulated inflammatory processes, such as Lupus.

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. Verdinexor was found to be generally safe and well tolerated. Mild to moderate AEs of similar number and grade 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, rare disease and autoimmune indications, including potentially partnering with a collaborator or through government-funded grant or contract opportunities.

Our Strategic Relationships

On January 24, 2018, we entered into an asset purchase agreement with Biogen pursuant to which Biogen acquired 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. KPT-350 is an IND-ready oral SINE compound with a preclinical data package supporting potential efficacy across a number of neurological, autoimmune and inflammatory conditions. XPO1 mediates the nuclear export of multiple proteins that impact neurological, autoimmune and inflammatory processes. Consequently, inhibition of XPO1 by KPT-350 results in a reduction in autoimmunity and 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, systemic lupus erythematosus and rheumatoid arthritis. We received a one-time upfront payment of $10 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 county-by-country basis.

Effective October 11, 2017, we entered into an exclusive license agreement with Ono Pharmaceutical Co., Ltd. (Ono), whereby Ono received rights to develop and commercialize selinexor and eltanexor (KPT-8602), 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 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$170.7 million at the exchange rate on the effective date of the agreement) 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, 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 oral, targeted therapy 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 March 1, 2018, we were the sole owner of 10 patents in the United States and we had 12 pending patent applications in the United States, four pending international applications filed under the Patent Cooperation Treaty (PCT), 31 granted patents and 123 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 March 1, 2018 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 three issued U.S. patents (one patent is specific to selinexor, and the two other patents cover both selinexor and verdinexor), 13 issued foreign patents, 45 pending foreign patent applications, two pending U.S. non-provisional application,

one directed to polymorphs of selinexor. 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 (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.

- **Selinexor (Wound Healing)**: Our patent portfolio covering selinexor for wound healing, including acute and chronic wounds, burns and scars, covers methods of using selinexor or verdinexor for wound healing, including systemic and topical uses, and consists of one pending U.S. application and one pending European application. Any patents that may issue in the United States 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. Any patents issued in Europe 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 three issued U.S. Patents that cover verdinexor. One patent is specific to verdinexor and the other two patents cover both verdinexor and selinexor (also referenced above with respect to selinexor).
- **Eltanexor** (**KPT-8602)**: Our eltanexor patent portfolio covers both the composition of matter and methods of use of eltanexor, and consists of one issued U.S. patent, one pending non-provisional U.S. patent application and 22 pending foreign patent applications. Any patents that may issue in the United States as part of our eltanexor patent portfolio 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.
- **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 nine patent families with one issued U.S. patent, one issued foreign patent, seven pending U.S. non-provisional patent applications, 23 pending foreign patent applications and two pending PCT applications in total. The PCT Applications provide the opportunity for seeking protection in all PCT member states. Any patents that may issue in the United States based on the pending U.S. non-provisional applications will expire in 2033 for the earliest filed application and 2034, 2035 or 2036 for the remaining applications, 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 2033, 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. Any patents that may issue in the United States based on the pending PCT applications will expire in 2036, 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 2036.

In addition to the patent portfolios covering our key drug candidates, as of March 1, 2018, our patent portfolio also includes four patents (U.S. Patent Nos. 8,513,230, 9,303,000, 9,428,490 and 9,550,757) and 17 granted foreign patents and pending patent applications in the U.S., PCT and foreign jurisdictions relating to other XPO1 inhibitors and their use in targeted therapeutics. We also filed three Intent to Use Trademark Applications on August 29, 2013 covering our name, our logo and the two used together. Marks for the name and name and logo together were registered in the United States on January 20, 2015 as Registration Nos. 4,676,255

and 4,676,226. The mark for our logo was registered in the United States on February 24, 2015 as Registration No. 4,693,107. As of March 1, 2018, we also have eleven pending Intent to Use Trademark Applications in the United States and a registration for PORE for our online portal. We have also filed applications for six drug names for selinexor outside the United States in sixteen jurisdictions, some of which have been registered.

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.

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, 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 with a projected primary completion date of October 2018, and it has indicated that it is planning a Phase 1 trial in hematologic malignancies.

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 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 that may be necessary for, our programs.

The key competitive factors affecting the success of all of our drug candidates, if approved, are likely to be their efficacy, safety, convenience, price, the availability of generic chemotherapy and other 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 that 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. If we obtain marketing approval for our drug candidates, 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.

If our lead drug candidates are approved for the indications of our initial focus, they may compete with the investigational therapies and currently marketed drugs discussed below.

Multiple Myeloma (MM)

Over the past 12 years, ten agents have been approved in the United States for the treatment of patients with MM: Velcade® (bortezomib, Takeda), Revlimid® (lenalidomide, Celgene), Thalomid® (thalidomide, Celgene), Doxil® (liposomal doxorubicin, Janssen), Kyprolis® (carfilzomib, Amgen), Pomalyst® (pomalidomide, Celgene), Farydak® (panobinostat, Novartis), Darzalex® (daratumumab, Janssen), Empliciti® (elotuzumab, BMS), and Ninlaro® (ixazomib, Takeda). Approved indications range from the treatment of newly diagnosed patients to those with relapsed and/or refractory MM.

Several other anti-cancer agents are in late-stage development for the treatment of patients with MM, including anti-B cell maturation antigen (BCMA), based CAR-T therapies such as bb2121 (Bluebird Bio/Celgene), JCHARHI25 (Juno Therapeutics/Celgene), P-BCMA-101 (Johnson & Johnson/Poseida Therapeutics), LCAR-B38M (Johnson & Johnson/Legend BioTech) and CART-BCMA (Novartis); monocolonal antibodies such as isatuximab (Sanofi); bi-specific antibodies such as GSK2857916 (GlaxoSmithKline) and PF-06863135 (Pfizer); and other novel agents such as ibrutinib (Abbvie/Roche), venetoclax (Abbvie), plitidepsin (PharMar), masitinib (AB Sciences), Opdivo® (nivolumab, BMS), filanesib (Array Biopharma), 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. Newer targeted agents such as the BTK inhibitor ibrutinib (Imbruvica®, Pharmacyclics) and the immunomodulatory drug lenalidomide (Revlimid®, Celgene) have 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, Gazyva® (obinutuzumab, Roche) Afinitor® (everolimus, Novartis), Revlimid® (lenalidomide, Celgene), Arzerra® (ofatumumab, GSK), Imbruvica® (ibrutinib, Pharmacyclics), venetoclax (Abbvie), acalabrutinib (Acerta Pharma), Opdivo® (nivolumab, BMS) and Adcetris® (brentuximab vendotin, Seattle Genetics). In addition, Yescarta (Kite/Gilead), a CAR-T therapy, has been approved as a treatment for patients with DLBCL and other CAR-T therapies are currently in clinical development.

Acute Myeloid Leukemia (AML)

Patients with AML typically are treated with intensive multi-agent chemotherapy, and high-risk patients who enter remission and have a matched donor often receive an allogeneic stem cell transplant. Because these chemotherapy regimens have marked toxicities, elderly patients with AML are often treated with less intensive chemotherapy regimens or drugs called hypomethylating agents such as Dacogen® (decitabine, Otsuka) or Vidaza® (azacitadine, Celgene). Once elderly patients with AML experience disease progression on their initial treatment, their expected survival is very poor. Because of their advanced age, multiple other medical conditions and requirements for multiple other drugs, the treatment of relapsed and/or refractory AML in elderly persons is complicated. Recently, new therapies for specific subsets of AML patients were approved, including midostaurin (Novartis), Vyxeos™/CPX-351 (cytarabine and daunorubicin liposome injection) (Jazz Pharmaceuticals) and IDHIFA® (Celgene/Agios Pharmaceuticals).

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. In December 2015, Stemline announced the opening of its IND application 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 with a projected primary completion date of October 2018, and it has indicated that it is planning a Phase 1 trial in hematologic malignancies. Additionally, Kosan Biosciences Inc. (acquired by Bristol-Myers Squibb Company) has 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 on which we plan to initially focus development 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. 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 selectively target PAK4 and/or NAMPT. 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 not aware of any 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 advanced into human clinical trials. These compounds include GMX1778 (also known as CHS-828), GMX1777 (water-soluble derivative of GMX1778), and APO866 (also known as FK866 and WK175). To our knowledge development of these inhibitors were discontinued. We are aware that NAMPT biology is being evaluated by Genentech, Inc., Eli Lilly & Company, Millennium/Takeda Pharmaceutical Company Ltd., OncoTartis, Inc., 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 rely, and expect to continue to rely, on third parties for the manufacture of our drug candidates for preclinical and clinical testing, as well as for commercial manufacture if our drug candidates receive marketing approval. We have engaged one third party manufacturer to obtain the active pharmaceutical ingredient for selinexor for preclinical and clinical testing. We have engaged a separate third-party manufacturer for fill-and-finish services. We obtain our selinexor supplies from these manufacturers on a purchase order basis and do not have a long-term supply arrangement in place at this time. We do not currently have arrangements in place for 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 a part of our commercialization plans.

All of our drug candidates are small molecules and are manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale up and does 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;
- 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. 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 good clinical practice, or 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.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

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

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

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

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

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

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious 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 2018 is $2,421,495 for an application requiring clinical data. The sponsor of an approved NDA is also subject to a program fee for fiscal year 2018 of $304,162. 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 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;
- 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 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. The new 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.

The 21st Century Cures Act

On December 13, 2016, President Obama signed the Cures Act into law. The Cures Act is designed to modernize and personalize healthcare, spur innovation and research, and streamline the discovery and development of new therapies through increased federal funding of particular programs. It authorizes increased funding for the FDA to spend on innovation projects. The new law also amends the Public Health Service Act to reauthorize and expand funding for the NIH. The Act establishes the NIH Innovation Fund to pay for the cost of development and implementation of a strategic plan, early stage investigators and research. It also charges NIH with leading and coordinating expanded pediatric research. Further, the Cures Act directs the Centers for Disease Control and Prevention to expand surveillance of neurological diseases.

With amendments to the FDCA and the Public Health Service Act, or PHSA, Title III of the Cures Act seeks to accelerate the discovery, development, and delivery of new medicines and medical technologies. To that end, and among other provisions, the Cures Act reauthorizes the existing priority review voucher program for certain drugs intended to treat rare pediatric diseases until 2020; creates a new priority review voucher program for drug applications determined to be material national security threat medical countermeasure applications; revises the FDCA to streamline review of combination product applications; requires FDA to evaluate the potential use of "real world evidence" to help support approval of new indications for approved drugs; provides a new "limited population" approval pathway for antibiotic and antifungal drugs intended to treat serious or life-threatening infections; and authorizes FDA to designate a drug as a "regenerative advanced therapy," thereby making it eligible for certain expedited review and approval designations.

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.

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.

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. According to the current plans of EMA, the new Clinical Trials Regulation will become applicable in 2019. The Clinical Trials Directive 2001/20/EC will, however, still apply three years from the date of entry into application of the Clinical Trials Regulation to (i) clinical trials applications submitted before the entry into application and (ii) clinical trials applications submitted within one year after the entry into application if the sponsor opts for old system.

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

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 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.

Brexit and the Regulatory Framework in the United Kingdom

In June 2016, the electorate in the United Kingdom voted in favor of leaving the EU (commonly referred to as Brexit). Thereafter, in March 2017, the country formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the EU will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to the EU Treaty. Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom.

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 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.

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 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;
- 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 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;
- 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 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 2013 and will stay in effect through 2024 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 any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent 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.

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 for any approved product and/or the level of reimbursement physicians receive for administering any approved product. Reductions in reimbursement levels may negatively impact the prices or the frequency with which 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. Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. In May 2017, the House of Representatives passed legislation known as the American Health Care Act of 2017. Thereafter, the Senate Republicans introduced and then updated a bill to replace the ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a "skinny" version of the Better Care Reconciliation Act of 2017. In addition, the Senate considered proposed healthcare reform legislation known as the Graham-Cassidy bill. None of these measures was passed by the Senate.

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.

More recently, with the December 2017 enactment of the Tax Cuts and Jobs Act of 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. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress will likely consider other legislation to replace elements of the ACA, during the next Congressional session.

Employees

As of March 1, 2018, we had 154 full-time employees, 114 of whom were primarily engaged in research and development activities and 40 of whom had an M.D. or Ph. degree.

Executive Officers of the Company

The following table lists the positions, names and ages of our executive officers as of March 1, 2018:

Name	Age	Position
Michael G. Kauffman, M.D., Ph.D.	54	Chief Executive Officer and Director
Sharon Shacham, Ph.D., M.B.A.	47	President and Chief Scientific Officer
Michael Falvey, M.S.M.	59	Executive Vice President, Chief Financial Officer and Treasurer
Ran Frenkel, RPh.	49	Chief Development Operations Officer
Christopher B. Primiano, J.D., M.B.A.	37	Executive Vice President, Chief Business Officer, General Counsel and Secretary

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 FDA 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, and on the board of directors and compensation committee and audit 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 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 (now Beth Israel Deaconess Medical Center) and Massachusetts General Hospitals. 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.

Michael Falvey, M.S.M. Mr. Falvey has served as Karyopharm's Chief Financial Officer since September 2017. Mr. Falvey has 35 years of financial management experience at leading biotechnology, technology and financial companies and has held Chief Financial Officer positions with both public and private companies. Most recently, Mr. Falvey served as Chief Financial Officer at Seven Bridges Genomics, Inc., a data and analytics platform provider, from August 2016 until June 2017. From July 2010 to April 2016, he served as Chief Financial and Administrative Officer for Analysis Group, a finance, economics and health care consulting firm. Prior to joining Analysis Group, Mr. Falvey served as Chief Financial Officer of Ahura Scientific Inc. and Aspect Medical Systems, Inc. and as Vice President, Finance of Millennium Pharmaceuticals Inc. Prior to Millennium, he also held financial positions at Fidelity Investments, Digital Equipment Corporation and General Electric. Mr. Falvey earned his Master of Science in Management from the Sloan School of Management at MIT, where he was also named a Seley Scholar. He earned his undergraduate degree from Georgetown University's School of Foreign Service.

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.

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 2017. 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.

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 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. You may also read and copy any materials we file with the SEC at the SEC’s Public Reference Room at 100 F Street, NE, Washington, DC 20549. Members of the public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains a website at http://www.sec.gov that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC.

Our Code of Business Conduct and Ethics, Corporate Governance Guidelines and the charters of the Audit, Compensation and Nominating and Corporate Governance 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 the Company 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 the Company. 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 Drug Candidates

We depend heavily on the success of our lead drug candidate selinexor (KPT-330), which is currently in clinical trials. Our clinical trials of selinexor may not be successful. If we are unable to commercialize selinexor or 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, which may not occur for several years, if ever, will depend heavily on the successful development, regulatory approval and eventual commercialization of selinexor.

We cannot commercialize drug candidates in the United States without first obtaining regulatory approval for the drug from the U.S. Food and Drug Administration, or FDA; similarly, we cannot commercialize drug candidates outside of the United States without obtaining regulatory approval from similar regulatory authorities outside of the United States. Even if selinexor or another drug candidate were to successfully obtain approval from the FDA and non-U.S. regulatory authorities, any approval might contain significant limitations related to use restrictions for specified age groups, warnings, precautions or contraindications, or may be subject to burdensome post-approval study or risk management requirements. If we are unable to obtain regulatory approval for selinexor in one or more jurisdictions, or any approval contains significant limitations, we may not be able to obtain sufficient funding or generate sufficient revenue to continue the development, marketing and/or commercialization of selinexor or any other drug candidate that we may discover, in-license, develop or acquire in the future. Furthermore, even if we obtain regulatory approval for selinexor, we will still need to develop a commercial organization, or collaborate with third parties for the commercialization of selinexor, establish commercially viable pricing and obtain approval for adequate reimbursement from third-party and government payors. If we or our commercialization collaborators are unable to successfully commercialize selinexor, we may not be able to generate sufficient revenues to continue 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.

We currently have no drugs approved for sale and we cannot guarantee that we will ever have marketable drugs. 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. For example, in 2016 we released top-line interim results from our Selinexor Treatment of Refractory Myeloma (STORM) study. While we believe the results we have observed to date are positive, there can be no assurance that further analysis will confirm our initial observations regarding this interim data or that data from the expansion of our STORM study will reflect similar results, or that results that we believe to be positive will be viewed similarly by regulatory authorities or as sufficient to support a request for registration.

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.

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 other 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 moderate 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 currently underway. We plan to seek 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 a primary endpoint 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. We are in the early stages of collecting clinical data in humans relating to the impact of selinexor on overall survival and comparative clinical data between selinexor and supportive care. If selinexor does not demonstrate an overall survival benefit, it will likely not be approved. 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 are doing 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 likely not be approved for that indication based on the applicable study.

We are early in our development efforts with a limited number of drug candidates in human clinical development. If we are unable to successfully develop and commercialize our drug candidates or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts and have four drug candidates, selinexor, verdinexor, eltanexor and KPT-9274, in clinical development for treatment of human diseases. The success of these and any of our other drug candidates will depend on several factors, including the following:

- 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;
- 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 drugs for which we may obtain marketing approval;
- launching commercial sales of the drugs, if and when approved, whether alone or in collaboration with others;
- acceptance of the drugs, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;

- obtaining and maintaining coverage and adequate reimbursement by third-party payors, including government payors, for any approved drugs;
- maintaining an acceptable safety profile of the drugs following approval;
- 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 our drug candidates, which would materially harm our business.

Our approach to the discovery and development of drug candidates that target Exportin 1, or XPO1, is unproven, and we do not know whether we will be able to develop any drugs of commercial value. If selinexor is unsuccessful in proving that drug candidates targeting XPO1 have commercial value or experiences significant delays in doing so, our business may be materially harmed.

Our SINE compounds inhibit the nuclear export protein XPO1. We believe that no currently approved cancer treatments are selectively targeting the restoration and increase in the levels of multiple tumor suppressor proteins in the nucleus. Despite promising results to date in preclinical studies of selinexor that we have conducted and in Phase 1 and Phase 2 clinical trials of selinexor conducted by us or our academic collaborators, we may not succeed in demonstrating safety and efficacy of SINE compounds in our current and future human clinical trials. Any drug candidates that we develop may not effectively prevent the exportation of tumor suppressor and/or growth regulatory proteins from the nucleus in humans with a particular form of cancer. If selinexor is unsuccessful in supporting the hypothesis that drug candidates targeting the regulation of intracellular transport of XPO1 have commercial value or experiences significant delays in doing so, our business may be materially harmed and we may not be able to generate sufficient revenues to continue our business.

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 our 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 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 drugs.

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 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;
- 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;
- 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.

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 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 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 or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for 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 during the development of our drug candidates or we observe limited efficacy of our drug candidates, we may need to abandon or limit the development of one or more of our drug candidates.

Four of our drug candidates are in clinical development for treatment of human diseases. Their risk of failure is high. It is impossible to predict when or if any of our drug candidates will prove effective or safe in humans or will receive marketing approval. If our drug candidates are associated with undesirable side effects or have characteristics that are unexpected, we may need to abandon their development or limit development 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. For example, we have modified our informed consent form and advised patients already enrolled in our clinical trials of the potential for worsening of pre-existing cataracts as a result of treatment with selinexor. Also, even though selinexor has generally been well-tolerated by patients in our clinical trials to date, in some cases there were adverse events, some of which were serious. The most common drug-related adverse events, or 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. A small percentage of patients have withdrawn from our clinical trials as a result of AEs. A small percentage of patients across our clinical trials have experienced serious adverse events, or 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.

As a result of these AEs or further safety or toxicity issues that we may experience in our clinical trials in the future, we may not receive approval to market any drug candidates, which could prevent us from ever generating revenue from the sale of drugs or achieving profitability. Results of our trials could reveal an unacceptably high severity and prevalence of side effects. In such an event, our trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us 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.

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.

Even if any of our drug candidates receives marketing approval, such drug 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.

If any of our drug candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. 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 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 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;
- sufficient third-party coverage or reimbursement;
- 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.

If, in the future, we are unable to establish sales and marketing capabilities or maintain current agreements or enter into additional agreements with third parties to sell and market our drug candidates, we may not be successful in commercializing our drug candidates if and when they are approved.

We are in the early stages of establishing a sales and marketing infrastructure and our company has not previously sold or marketed 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 and marketing organization or outsource these functions to other third parties. In the future, we may choose to build a sales and marketing 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 and marketing of our drug candidates. We are currently establishing the commercial infrastructure to support a potential launch of selinexor in the United States, and we intend to work with existing and potential partners to establish such commercial infrastructure outside the United States.

There are risks involved with both establishing our own sales and marketing 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. If the commercial launch of a drug candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, 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 our drugs on our own include:

- our inability to recruit 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 and marketing 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 and market 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 and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our drug candidates.

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

Our license agreements provide for payments on achievement of development and/or commercialization milestones and for royalties on product sales. However, because none of our drug candidates have been approved for commercial sale, our drug candidates are at early stages of development and drug development entails a high risk of failure, we may never realize any material portion of the milestone revenue provided in our license 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 our current 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 if our drug candidates are approved, they 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 competitors may develop 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 commercialize any drug candidates, 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 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.

Significant uncertainty exists as to the coverage and reimbursement status of our product candidates for which we seek regulatory approval. Our ability to commercialize any drugs 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 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, if they are approved, 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 any drug 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, 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 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 cause us to incur substantial liabilities and to limit commercialization of any 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 and will face an even greater risk if we commercially sell any drugs that we may develop. If we cannot successfully defend ourselves against claims that our drug candidates or drugs caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any drug candidates or drugs that we may develop;
- injury to our reputation and significant negative media attention;

- withdrawal of clinical trial participants;
- 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 commercialize any drugs that we may develop.

We currently hold clinical trial liability insurance coverage, but that coverage may not be adequate to cover any and all liabilities that we may incur. We would need to increase our insurance coverage when we begin the commercialization of our drug candidates, if ever. 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;
- 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 and Need for Additional Capital

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

Since inception, we have incurred significant operating losses. Our net losses were $129.0 million, $109.6 million and $118.2 million for the years ended December 31, 2017, December 31, 2016 and December 31, 2015, respectively. As of December 31, 2017 and December 31, 2016, we had an accumulated deficit of $495.3 million and $366.1 million, respectively. We have not generated any revenue to date from sales

of any drugs 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 and cash generated from our business development activities. We have devoted substantially all of our efforts to research and development. Our lead drug candidate, oral selinexor, as well as verdinexor, eltanexor and KPT-9274, are in clinical development. As a result, we expect that it will be several years, if ever, before we have a drug candidate ready for commercialization for the treatment of human disease. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

- 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;
- establish a sales, marketing and distribution infrastructure to commercialize any drugs for which we may obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- manufacture our drug candidates;
- hire additional clinical, quality control and scientific personnel;
- identify additional drug candidates;
- acquire or in-license other drugs and technologies; and
- add operational, financial and management information systems and personnel, including personnel to support our drug development, any future commercialization efforts and our other operations as a public company.

To become and remain profitable, we must develop and eventually commercialize a drug or drugs with significant market potential, either on our own or with a collaborator. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our drug candidates, obtaining marketing approval for these drug candidates, manufacturing, marketing and selling those drugs for which we may obtain marketing approval and establishing and managing any collaborations for the development, marketing and/or commercialization of our drug candidates. We may never succeed in these activities and, even if we do, may never generate revenues that are significant or large enough to achieve profitability. 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 the 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.

Our short 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 and conducting preclinical studies and early-phase and later-phase clinical trials of our drug candidates. Our lead drug candidate is currently in multiple Phase 2 and Phase 3 clinical trials and all of our other drug candidates for the treatment of human disease are in early clinical development. We have not yet demonstrated our ability to successfully complete any late-phase clinical trials in humans, including large-scale clinical trials, obtain marketing approvals, manufacture a commercial scale drug, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful drug commercialization. Typically, it takes about six to ten years to develop one new drug from the time it is in Phase 1 clinical trials to when it is commercially available for treating patients. 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 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 continue the clinical trials of, and seek marketing approval for, selinexor and our other drug candidates. In addition, if we obtain marketing approval for any of our drug candidates, we expect to incur significant commercialization expenses related to drug sales, marketing, manufacturing and distribution 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. Furthermore, we will 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 drug development programs or commercialization efforts.

We expect that our existing cash, cash equivalents and investments will enable us to fund our current operating and capital expenditure plans through at least the first quarter of 2019 while we are establishing the commercial infrastructure for a potential launch of selinexor in the United States. Our future capital requirements will depend on many factors, including:

- 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;
- 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 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, if any, received from commercial sales of our drug candidates, should any of our drug candidates receive marketing approval; and
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

Identifying potential drug candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve drug sales. In addition, our drug

candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available for at least one or possibly many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. 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.

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.

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 commercialization efforts or grant rights to develop and market drug candidates that we would otherwise prefer to develop and market ourselves.

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

Global credit and financial markets have experienced extreme disruptions over some of the past several years. Such disruptions have resulted, and could in the future result, in diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. 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.

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 a collaboration with Ono Pharmaceutical Co., Ltd., and will continue to seek

to enter into additional collaborations, 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 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;
- 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 proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- 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 the 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 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.

Our drug development programs and the potential commercialization of our drug candidates 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 and/or 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 its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms, or at all. If we do not have sufficient funds, we may not be able to further develop 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 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 EMA also requires us to comply with comparable standards. 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.

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.

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 other 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 for clinical trials and ultimately for commercialization. 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 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 expect to rely on third-party manufacturers or third-party collaborators for the manufacture of our drug candidates for clinical trials and ultimately for commercial supply of any of these drug candidates for which we or any of our collaborators obtain marketing approval. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- 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 drug candidate according to our schedule, or at all, including if the third-party manufacturer gives greater priority to the supply of other drugs over our drug candidates or otherwise does not satisfactorily perform according to the terms of the manufacturing agreement;
- 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.

Third-party manufacturers may not be able to comply with current Good Manufacturing Practices, or cGMP, regulations or similar regulatory requirements outside of the United States. As with all drug manufacturing, our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of drug candidates or drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our drugs and harm our business 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 or marketing approval. 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, 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 our drug candidates or drugs 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 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 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. To date, 39 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, two patents have issued that relate to our PAK4/NAMPT inhibitor, KPT-9274, including a composition of matter patent 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 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 a third party 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 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 and marketing our drug candidates and using our 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 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 March 1, 2018, four of our trademarks are registered in the United States. We also have eleven pending intent-to-use applications in the United States, some of which have been allowed, meaning that we can perfect our registrations when we have commenced use in commerce. Outside the United States, we have registrations in the European Union for five trademarks (drug names for selinexor), pending applications for those same five marks and a pending application for a sixth. Applications for the same six trademarks were filed in 15 other jurisdictions, some of which have also proceeded to registration. 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.

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 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. Our drug candidates are in early stages of development and are subject to the risks of failure inherent in drug development. We have not submitted an application for or received marketing approval for 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.

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.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

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 multiple myeloma and 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. Assuming positive results from our expanded STORM study and remaining unmet medical need, we intend to use the data from the expanded study to support a request that the FDA consider granting accelerated approval for selinexor in penta-refractory multiple myeloma. The FDA has reiterated to us in its feedback that accelerated approval is available only for drugs that provide a meaningful therapeutic benefit over existing treatments at the time of consideration of the application for accelerated approval. Any experimental or approved therapies showing activity in patients with penta-refractory multiple myeloma that may exist at the time the FDA acts on any request we may make for accelerated approval could cause the FDA to deny our request. In addition, the FDA has indicated that additional therapies may receive full approval in multiple myeloma prior to the submission of a New Drug Application, or NDA, by us, which could mean that, at the time the FDA takes action on our accelerated approval submission, treatment of

the penta-refractory group is no longer considered an unmet medical need or a patient population that has exhausted available therapies. The FDA has recommended that we plan for regular approval based on a randomized trial for the evaluation of safety and efficacy of selinexor for the treatment of multiple myeloma, and has previously indicated to us its preference for studies that isolate the effects of individual drugs. Although we believe that the STORM study design and the expansion in the penta-refractory patient group present an opportunity for us to request that the FDA grant accelerated approval if data from our Phase 2b STORM study support such an application, there can be no assurance that the FDA will grant such approval, whether on an accelerated basis, or at all.

Similarly, assuming positive results from our SADAL study and remaining unmet medical need, we intend to use the data from the study to support a request that the FDA consider granting accelerated approval for selinexor in relapsed and/or refractory DLBCL. While the FDA agreed that the current 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. 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 if data from our SADAL study support such an application, 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 an NDA 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, if we decide to submit an application for accelerated approval or under another expedited regulatory designation, there can be no assurance that such submission or application will be accepted or that any expedited development, review or approval will be granted on a timely basis, or at all.

Moreover, 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. 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 may submit to the European Medicines Agency, or EMA, to support conditional approval of selinexor to treat penta-refractory multiple myeloma, relapsed/refractory diffuse large B-cell lymphoma, or any other cancer indication. 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 for commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

A fast track designation, grant of priority review status 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, priority review 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. If a product offers major advances in

treatment, the product sponsor may apply for FDA priority review status. 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.

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 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 selinexor in AML, diffuse large B-cell lymphoma, or DLBCL, and multiple myeloma, 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 (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 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.

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.

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, 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;
- 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.

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 any drugs 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.

In March 2010, Congress enacted the Patient Protection and Affordable Care Act, or ACA. Among the provisions of the ACA of potential importance to our business and our drug candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- 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% 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 2013 and will stay in effect through 2024 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 any of our product candidates for which we may obtain regulatory approval or the frequency with which 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 any 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. Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. In May 2017, the House of Representatives passed legislation known as the American Health Care Act of 2017. Thereafter, the Senate Republicans introduced and then updated a bill to replace the ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a “skinny” version of the Better Care Reconciliation Act of 2017. In addition, the Senate considered proposed healthcare reform legislation known as the Graham-Cassidy bill. None of these measures was passed by the Senate.

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.

More recently, with the December 2017 enactment of the Tax Cuts and Jobs Act of 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. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress will likely consider other legislation to replace elements of the ACA, during the next Congressional session.

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 product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop commercialize product candidates.

The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Administration have stated that they will address such costs through new legislative and administrative measures. The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

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 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 $5,500 to $11,000 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 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.

The collection and use of personal health data of individuals in the European Union is governed by strict data protection laws. The Data Protection Directive imposes several requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities and the security and confidentiality of the personal data. The Data Protection Directive also imposes strict rules on the transfer of personal data out of the European Union to the United States. Failure to comply with the requirements of the Data Protection Directive and the related national data protection laws of the European Union Member States may result in fines and other administrative penalties. In addition to existing laws, from May 25, 2018, the stricter General Data Protection Regulation will replace the current Data Protection Directive. The regulation introduces new

obligations with respect to European Union data and substantial fines for breaches of the data protection rules. It will increase our responsibility and potential liability in relation to personal data that we process and we will be required to put in place additional mechanisms ensuring compliance with the new European Union data protection rules. This may be onerous and adversely affect our business, financial condition, results of operations and prospects.

Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including 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 we have established, 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. 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 or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business 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 the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. 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 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.

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

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs and sales and marketing. To manage our 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 a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The physical 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. For example, the loss of clinical trial data from 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 results 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 could be damaged, and the further development of our drug candidates could be delayed. 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, 2017, 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;
- 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 $4.83. On March 9, 2018, the closing sale price of our common stock on The Nasdaq Global Select Market was $16.86 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:

- the success of competitive drugs or technologies;
- results of clinical trials of our drug candidates or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our drug candidates or clinical development programs;
- 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.

We could be subject to securities class action litigation.

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. If we face such litigation, it could result in substantial costs and a diversion of management's attention and our resources, which could harm our business.

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.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company through 2018. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, reduced disclosure obligations regarding executive compensation and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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

As a public company, and particularly after we are no longer an "emerging growth company," we will 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 will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly.

We cannot predict with certainty the amount of additional costs we may incur to continue to operate as a public company, nor can we predict the timing of such costs. In addition, the rules and regulations applicable to

public companies are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies which could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we are not required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps 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 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. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. In addition, 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. We had 49,533,150 shares outstanding as of December 31, 2017. Of such shares, at least 10.3 million shares 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.

Moreover, holders of an aggregate of at least 10.5 million shares of our common stock as of December 31, 2017 have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. 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

state tax authorities under relevant state tax rules). In addition, as a result of the Tax Cuts and Jobs Act of 2017, 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 newly enacted federal tax law. 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 recently passed comprehensive tax reform bill could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law new legislation that significantly revises the Internal Revenue Code of 1986, as amended. The newly enacted federal income tax law, 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 newly enacted federal tax law.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our headquarters are located in Newton, Massachusetts, where we lease 62,143 square feet of office and laboratory space. We also lease approximately 3,681 square feet of office space in Munich, Germany.

Item 3. Legal Proceedings

We are not a party to any material legal proceedings.

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."

Price Range of Our Common Stock

The following table sets forth the reported high and low sales prices of our common stock as reported on the Nasdaq Global Select Market for each quarter in the years ended December 31, 2017 and 2016:

	Year Ended December 31, 2017	
	High	Low
First Quarter	$ 14.63	$ 9.06
Second Quarter	$ 13.19	$ 7.48
Third Quarter	$ 11.74	$ 8.00
Fourth Quarter	$ 12.56	$ 9.00

	Year Ended December 31, 2016	
	High	Low
First Quarter	$ 13.97	$ 4.83
Second Quarter	$ 10.45	$ 6.63
Third Quarter	$ 11.41	$ 6.54
Fourth Quarter	$ 10.30	$ 6.27

Holders

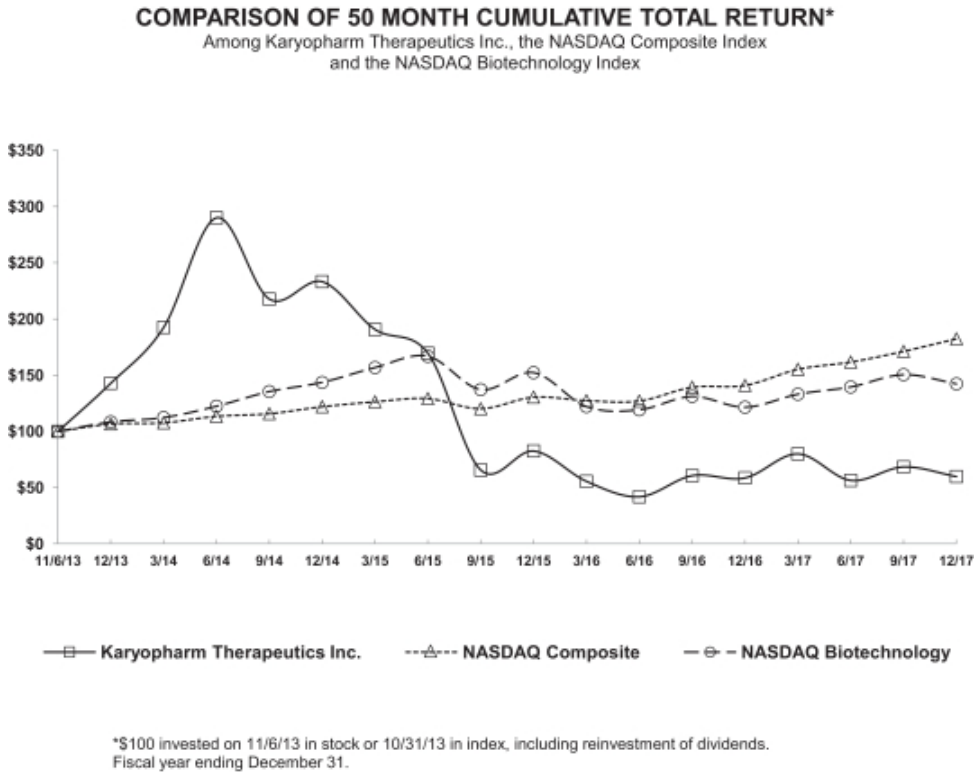
As of March 1, 2018, there were 11 holders of record of our common stock.

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.

Stock Performance Graph

The following graph shows a comparison from November 6, 2013, the date on which our common stock first began trading on the Nasdaq Global Select Market, through December 31, 2017, of the cumulative total return on an assumed investment of $100.00 in cash in our common stock as compared to the same investment in the NASDAQ Composite Index and the NASDAQ Biotechnology Index. Such returns are based on historical results and are not intended to suggest future performance. Data for the NASDAQ Composite Index and NASDAQ Biotechnology Index assume reinvestment of dividends.



Cumulative Total Return Comparison

	11/6/13	12/31/13	12/31/14	12/31/15	12/31/16	12/31/17
Karyopharm Therapeutics Inc.	**100.00**	**142.80**	**233.21**	**82.55**	**58.57**	**59.81**
NASDAQ Composite	**100.00**	**106.62**	**122.02**	**130.48**	**140.92**	**182.40**
NASDAQ Biotechnology	**100.00**	**108.49**	**143.56**	**152.27**	**121.51**	**142.30**

The performance graph in this Item 5 is not deemed to be “soliciting material” or to be “filed” with the SEC for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed incorporated by reference into any filing of Karyopharm Therapeutics Inc. under the Securities Act or the Exchange Act, except to the extent we specifically incorporate it by reference into such a filing.

Recent Sales of Unregistered Securities

None.

Item 6. Selected Financial Data

You should read the following selected financial data together with our consolidated financial statements and the related notes appearing elsewhere in this Annual Report on Form 10-K and the "Management's discussion and analysis of financial condition and results of operations" section of this Annual Report on Form 10-K. The selected historical financial information in this section is not intended to replace our financial statements and the related notes therein. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

	Years Ended December 31,				
	2017	2016	2015	2014	2013
	(In thousands, except share and per share amounts)				
Consolidated Statement of Operations Data:					
License and other revenue	$ 1,605	$ 154	$ 250	$ 229	$ 387
Operating expenses:					
Research and development	107,273	86,938	97,744	60,127	28,452
General and administrative	24,870	23,948	21,582	15,948	5,885
Total operating expenses	132,143	110,886	119,326	76,075	34,337
Loss from operations	(130,538)	(110,732)	(119,076)	(75,846)	(33,950)
Other income, net	1,617	1,294	895	69	3
Loss before income taxes	(128,921)	(109,438)	(118,181)	(75,777)	(33,947)
Provision for income taxes	(63)	(139)	—	—	—
Net loss	$ (128,984)	$ (109,577)	$ (118,181)	$ (75,777)	$ (33,947)
Net loss per share—basic and diluted	$ (2.81)	$ (2.92)	$ (3.32)	$ (2.43)	$ (5.59)
Weighted-average number of common shares used in net loss per share—basic and diluted	45,899,784	37,523,051	35,619,506	31,135,694	6,067,679

	As of December 31,				
	2017	2016	2015	2014	2013
	(in thousands)				
Consolidated Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 146,469	$ 129,552	$ 175,633	$ 205,724	$ 155,974
Working capital	98,956	115,160	162,468	195,450	154,664
Total assets	180,294	180,385	215,443	220,337	158,226
Total preferred stock and preferred stock subscription	—	—	—	—	—
Total stockholders' equity	129,464	162,243	198,365	206,794	154,934

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 a clinical-stage pharmaceutical company focused on the discovery, development and subsequent 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 focused on understanding the regulation of intracellular communication between the nucleus and the cytoplasm. We have discovered and are developing wholly-owned, novel, small molecule **Selective Inhibitor of Nuclear Export** (**SINE**) compounds that inhibit the nuclear export protein exportin 1 (XPO1). These SINE compounds represent a new class of drug candidates with a novel mechanism of action that have the potential to treat a variety of diseases in areas of unmet medical need. Our SINE compounds were the first oral XPO1 inhibitors in clinical development.

Our focus is on seeking the regulatory approval and commercialization of our lead drug candidate, selinexor (KPT-330), as an oral agent in cancer indications with significant unmet clinical need, initially for hematologic malignancies. We then plan to seek additional approvals for the use of selinexor in combination therapies to expand the patient populations that are eligible for selinexor, as well as to move selinexor towards front-line cancer therapy. We are also advancing the clinical development of selinexor in multiple solid tumor indications. To date, over 2,200 patients have been treated with oral selinexor in company- and investigator-sponsored clinical trials in advanced hematologic malignancies and solid tumors. Selinexor is currently being evaluated in several later-stage clinical trials, including, among others, the Phase 2b STORM (**S**elinexor **T**reatment **o**f **R**efractory **M**yeloma) study in multiple myeloma, the Phase 1b/2 STOMP (**S**elinexor and Backbone **T**reatments **o**f **M**ultiple Myeloma **P**atients) study in combination with standard therapies in multiple myeloma, the Phase 2b SADAL (**S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma) study in diffuse large B-cell lymphoma (DLBCL), the pivotal, randomized Phase 3 BOSTON (**Bo**rtezomib, **S**elinexor and Dexame**t**has**one**) study in multiple myeloma, and the Phase 2/3 SEAL (**Se**linexor in **A**dvanced **L**iposarcoma) study in liposarcoma.

We expect to provide top-line data from the expanded cohort for the STORM study at the end of April 2018, top-line data from the SADAL study by the end of 2018, top-line data from the BOSTON study in 2019 and top-line data from the Phase 3 portion of the SEAL study by the end of 2019. We are also establishing the commercial infrastructure to support a potential launch of selinexor in the United States and we intend to work with existing and potential partners to establish such commercial infrastructure outside the United States. To date, we 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 and cash generated from our business development activities.

As of December 31, 2017, we had an accumulated deficit of $495.3 million. We had net losses of $129.0 million, $109.6 million and $118.2 million for the years ended December 31, 2017, 2016 and 2015, respectively. We have not generated any revenue to date from sales of any drugs.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

- 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;
- establish a sales, marketing and distribution infrastructure to commercialize any drugs for which we may obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- manufacture our drug candidates;

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

Financial Overview

Revenue Recognition

To date, we have not generated any revenue from drug sales. Our ability to generate revenues from drug sales will depend on the successful development and eventual commercialization of our drug candidates.

To date, our revenue has been from license arrangements as well as foundation and government grants and contracts.

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 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 in the financial statements as prepaid or accrued research and development.

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 IND-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.

General and Administrative Expenses

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.

We anticipate that our general and administrative expenses will increase in the future to support continued research and development activities, potential commercialization of our drug candidates and increased costs of operating as a public company. 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.

Other Income (Expense)

Other income consists primarily of interest income earned on our cash and cash equivalents and short-term and long-term investments. Other expense consists primarily of foreign currency transaction losses associated with our German subsidiary whose functional currency is the Euro.

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 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.

Collaboration and License Agreements

We generate revenue from collaboration and license agreements with pharmaceutical companies for the development and commercialization of certain of our product candidates. Collaboration and license agreements may include non-refundable upfront payments, reimbursement of research and development services and costs, payments based upon the achievement of defined milestones, license fees and profit share and/or royalties on sales of product candidates if they are successfully approved and commercialized. Our performance obligations under the collaborations may include the transfer of intellectual property rights in the form of licenses, obligations to provide research and development services and participation on certain committees with the licensor. We make judgments that affect the periods over which we recognize revenue.

We evaluate multiple element agreements under the Financial Accounting Standards Board (FASB) Accounting Standards Codification (ASC) Revenue Recognition (Topic 605). When evaluating multiple element arrangements under Topic 605, we identify the deliverables included within the agreement and determines whether the deliverables under the arrangement represent separate units of accounting. Deliverables under the arrangement are a separate unit of accounting if (i) the delivered item has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item and delivery or performance of the undelivered items are considered probable and substantially within our control. This evaluation requires subjective determinations and requires management to make judgments about the individual deliverables and whether such deliverables are separable from the other aspects of the contractual relationship. In determining the units of accounting, management evaluates certain criteria, including whether the deliverables have standalone value, based on the consideration of the relevant facts and circumstances for each arrangement.

We consider whether the licensor can use the license or other deliverables for their intended purpose without the receipt of the remaining elements, whether the value of the deliverable is dependent on the undelivered items and whether there are other vendors that can provide the undelivered items.

Arrangement consideration generally includes up-front license fees. We determine how to allocate arrangement consideration to identified units of accounting based on the selling price hierarchy provided under the relevant guidance. We determine the estimated selling price for deliverables using vendor-specific objective evidence (VSOE) of selling price, if available, third-party evidence (TPE), if VSOE is not available, or best estimate of selling price (BESP), if neither VSOE nor TPE is available. Determining the BESP for a deliverable requires significant judgment. The estimated selling prices may be based on similar license arrangements, the nature of the research and development services to be performed and market rates for similar services.

Up-front payments received in connection with licenses of our technology rights are deferred if facts and circumstances dictate that the license does not have stand-alone value. When management believes the license to its intellectual property does not have stand-alone value from the other deliverables to be provided in the

arrangement, it is combined with other deliverables and the revenue of the combined unit of accounting is recorded based on the method appropriate for the last delivered item. We executed two license agreements during 2017. In both arrangements, the license was determined not to have stand-alone value and was combined with other deliverables. In one agreement, we determined that the final deliverable, the technology knowledge transfer, was provided and recognized $1.25 million related to the up-front payment at the time of delivery in the fourth quarter of 2017. In the case of the other agreement, the final deliverable was not provided as of December 31, 2017 and therefore, the up-front payment of ¥2.5 billion (US$21.9 million on the date received) has not been recognized as revenue in 2017. See Note 7, “Collaboration and License Agreements”.

We adopted ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)* on January 1, 2018.

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.

Stock-based Compensation

We issue stock-based awards to employees and non-employees, generally in the form of stock options, restricted stock and restricted stock units. We account for our stock-based awards to employees in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation* (ASC 718). ASC 718 requires all stock-based awards to employees, including grants of employee stock options and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. We account for stock-based awards to non-employees in accordance with FASB ASC Topic 505-50, *Equity-Based Payments to Non-Employees*, which requires the award to be re-measured at fair value as the award vests. We recognize the compensation cost of stock-based awards to employees on a straight-line basis over the vesting period of the award and by using an accelerated attribution model for awards to non-employees. Described below is the methodology we have utilized in measuring stock-based compensation expense.

We estimate the fair value of our options to employees and non-employees using the Black-Scholes option pricing model, which requires the input of assumptions, including (a) the expected volatility of our stock, (b) the

expected term of the option, (c) the risk-free interest rate, and (d) expected dividends. Due to our lack of sufficient history as a public company, we estimate the volatility of our common stock price based on the historical volatility of a group of representative companies that are publicly traded. For these analyses, we select companies with comparable characteristics to 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. We compute the historical volatility data using the closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our options. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We estimate the expected term of our employee stock options using the "simplified" method pursuant to Staff Accounting Bulletin No. 107 *Share-based payments*, whereby the expected term equals the average of the vesting term and the original contractual term of the option. For non-employee stock options, we utilize the contractual term of the option. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury yield curve in effect during the period the options were granted. We have not paid and do not anticipate paying cash dividends on our shares of common stock; therefore, the expected dividend yield is assumed to be zero. Subsequent to adoption of ASU 2016-09, *Compensation—Stock Compensation (Topic 718)*, on January 1, 2017, as described below in *Recently Issued Accounting Pronouncements*, forfeitures are recognized as they occur.

For performance-based restricted stock, at each reporting period we assess the probability that the performance condition(s) will be achieved. We use the accelerated attribution method to expense the awards over the implicit service period based on the probability of achieving the performance conditions. We estimate the implicit service period based on our best estimate of the period over which an award's vesting condition(s) will be achieved. We review and evaluate these estimates on a quarterly basis and will recognize any remaining unrecognized compensation expense as of the date of an estimate revision over the revised remaining implicit service period.

Results of Operations

The following table summarizes our results of operations for the years ended December 31, 2017, 2016 and 2015:

	Years Ended December 31,		
	2017	2016	2015
	(in thousands)		
Contract and grant revenue	$ 1,605	$ 154	$ 250
Operating expenses:			
Research and development	107,273	86,938	97,744
General and administrative	24,870	23,948	21,582
Loss from operations	(130,538)	(110,732)	(119,076)
Other income, net	1,617	1,294	895
Loss before income taxes	(128,921)	(109,438)	(118,181)
Provision for income taxes	(63)	(139)	—
Net loss	$(128,984)	$(109,577)	$(118,181)

Comparison of Years Ended December 31, 2017 and 2016

License and Other Revenue. We recognized revenue pursuant to a license agreement with Anivive Lifesciences, Inc., or Anivive, and government grants in 2017 and pursuant to a government grant in 2016. Revenue for the year ended December 31, 2017 was $1.6 million compared to $0.2 million for the year ended December 31, 2016. The increase in revenue during the year ended December 31, 2017 was primarily the result

of entering into the license agreement with Anivive in April 2017 and the satisfaction of the related revenue recognition criterion, in October 2017, which resulted in revenues of $1.25 million.

Research and Development Expense. Research and development expense increased by approximately $20.4 million to $107.3 million for the year ended December 31, 2017 from $86.9 million for the year ended December 31, 2016. The increase was primarily related to:

- an increase of approximately $13.3 million in clinical trial costs, primarily related to the selinexor program;
- an increase of $3.0 million in consulting and professional expense;
- an increase of $2.2 million in expenses primarily related to our obligation to pay a portion of upfront fees received from license agreements;
- an increase of $2.1 million in personnel costs, primarily due to increased headcount and compensation increases, offset by decreased stock-based compensation expense of $0.9 million; and
- an increase of $0.8 million in travel, toxicology study costs and other expenses;
- partially offset by a decrease of $1.0 million in discovery and occupancy costs.

We expect our research and development expenses to continue to increase for the full year 2018 compared with the prior year as we continue spending on our development programs and clinical trials, including the continued clinical development of selinexor in our lead indications with a focus on submission of an NDA with the FDA requesting accelerated approval in penta-refractory multiple myeloma during 2018, assuming a positive outcome from the expanded cohort of the STORM study.

General and Administrative Expense. General and administrative expense increased by approximately $1.0 million to approximately $24.9 million for the year ended December 31, 2017 from approximately $23.9 million for the year ended December 31, 2016. The increase was primarily related to:

- an increase of approximately $0.7 million in personnel costs, primarily due to increased headcount, offset by a decrease of approximately $0.9 million in stock-based compensation expense related to equity awards granted to personnel and non-employees; and
- an increase in consulting, occupancy and travel costs of $0.6 million;
- partially offset by a decrease of $0.3 million in other costs.

We expect our general and administrative expenses to increase in the future in support of our expanding operating and commercial activities.

Other Income, net. Other income, net increased by approximately $0.3 million to approximately $1.6 million for the year ended December 31, 2017 from $1.3 million for the year ended December 31, 2016. The increase is primarily due to increased returns resulting from a general increase in interest rates.

Comparison of Years Ended December 31, 2016 and 2015

Contract and Grant Revenue. We recognized revenue pursuant to a government grant in 2016 and pursuant to a sponsored research agreement in 2015. Contract and grant revenue for the year ended December 31, 2016 was $0.2 million compared to $0.3 million for the year ended December 31, 2015. The decrease in revenue was the result of recognizing less revenue pursuant to grant funding during the year ended December 31, 2016.

Research and Development Expense. Research and development expense decreased by approximately $10.8 million to $86.9 million for the year ended December 31, 2016 from $97.7 million for the year ended December 31, 2015. The decrease is primarily related to:

- a decrease of approximately $7.7 million in clinical trial costs, of which $5.9 million relates to selinexor clinical trial costs due to timing of clinical trial enrollment and clinical trial supply work completed in 2015;
- a decrease of $4.7 million in preclinical efficacy and toxicology study costs;
- a decrease of $3.2 million in consulting and professional expense, which includes an increase of $0.5 million in stock-based compensation expense related to equity awards granted to non-employees;
- a decrease of $2.2 million in discovery expense; and
- a decrease of $1.4 million in travel and collaboration expenses;
- partially offset by an increase of $7.9 million in personnel costs, primarily due to increased headcount, and an increase of $3.3 million in stock-based compensation expense related to equity awards granted to personnel; and
- an increase of $0.5 million in occupancy depreciation and other expenses.

General and Administrative Expense. General and administrative expense increased by approximately $2.4 million to approximately $23.9 million for the year ended December 31, 2016 from approximately $21.6 million for the year ended December 31, 2015. The increase is primarily related to:

- an increase of approximately $3.3 million in personnel costs, primarily due to increased headcount and an increase of approximately $1.5 million in stock-based compensation expense related to equity awards granted to personnel;
- partially offset by a decrease of approximately $0.6 million in consulting and professional expense; and
- a decrease of $0.3 million in occupancy, travel and other expense.

Other Income, net. Other income, net increased by approximately $0.4 million to approximately $1.3 million for the year ended December 31, 2016, from $0.9 million for the year ended December 31, 2015. The increase is primarily related to interest income earned on our investments.

Liquidity and Capital Resources

To date, we have not generated material revenues. We 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 and cash generated from our business development activities.

As of December 31, 2017, we had $175.9 million in cash, cash equivalents and short- and long-term investments. In January 2015, we completed an underwritten offering of 2,950,000 shares of our common stock at public price of $33.00 per share. We received net proceeds of approximately $90.8 million, after deducting the underwriting discount and offering expenses payable by us. In December 2015, we entered into a sales agreement (Agreement), relating to an “at-the-market” offering, pursuant to which we issued and sold shares of our common stock with an aggregate offering price of up to $50.0 million. On November 7, 2016, we entered into an amendment to the Agreement pursuant to which we issued and sold shares of our common stock with an additional aggregate offering price of up to $50.0 million on or after November 7, 2016. On December 1, 2017, we entered into a second amendment to the Agreement pursuant to which we may issue and sell shares of our common stock having an additional aggregate offering price of up to $75.0 million on or after December 1, 2017. As of December 31, 2017, we had sold an aggregate of 9,172,159 shares pursuant to this “at-the-market” offering, for net proceeds of approximately $89.1 million. There have been no sales pursuant to this

“at-the-market” offering during 2018. 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 our 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 discounts and commissions and offering expenses payable by us.

On October 11, 2017 (Effective Date), we entered into a license agreement (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, or 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 (Ono Territory). Pursuant to the terms of the 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 (US$90.5 million at the exchange rate as of the Effective Date) in milestone payments if certain development goals are achieved and up to ¥9.0 billion (US$80.2 million at the exchange rate as of the 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.

On January 24, 2018, we entered into an Asset Purchase Agreement (APA), with Biogen MA Inc., a Massachusetts corporation and subsidiary of Biogen, Inc. (Biogen), pursuant to which Biogen acquired 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).

Under the terms of the APA, Biogen purchased KPT-350 and certain related assets and assumed certain related liabilities. We received a one-time upfront payment of $10.0 million from Biogen and are eligible to receive additional payments of up to $207.0 million based on the achievement by Biogen of future specified development and commercial milestones. We are also eligible to receive tiered royalty payments that reach low double digits based on future net sales until the later of the tenth anniversary of the first commercial sale of the applicable product and the expiration of specified patent protection for the applicable product, determined on a country-by-country basis.

We are a party to a research agreement with the Multiple Myeloma Research Foundation (MMRF). Under this research agreement, we are obligated to make certain payments to MMRF, including payments in the event we out-license selinexor. The terms of this research agreement do not apply to eltanexor. In connection with the transactions contemplated under the License Agreement, we paid to MMRF approximately ¥225 million (approximately US$2.0 million) of the upfront cash payment from Ono, and we are obligated to pay a percentage of any milestone payments from Ono and a mid-single-digit percentage of any royalty payments from Ono. The maximum aggregate amount we may be obligated to pay to MMRF under the research agreement is $6.0 million.

We expect that our cash, cash equivalents and short- and long-term investments as of December 31, 2017, totaling $175.9 million, along with the $10.0 million received from Biogen in 2018, will be sufficient to fund our current operating plans and capital expenditure requirements through at least the first quarter of 2019 while we are establishing the commercial infrastructure for a potential launch of selinexor in the United States.

Cash flows

The following table provides information regarding our cash flows:

	Years Ended December 31,		
	2017	2016	2015
		(in thousands)	
Net cash used in operating activities	$(73,717)	$(84,391)	$(94,029)
Net cash provided by (used in) investing activities	17,108	24,595	(90,823)
Net cash provided by financing activities	75,743	51,164	92,700
Effect of exchange rate changes	200	(63)	(99)
Net increase (decrease) in cash and cash equivalents	$ 19,334	$ (8,695)	$(92,251)

Net Cash Used in Operating Activities

Net cash used in operating activities was $73.7 million during the year ended December 31, 2017 compared to $84.4 million during the year ended December 31, 2016. Net cash used in operating activities in both periods resulted primarily from our net losses adjusted for non-cash charges and changes in the components of working capital. The decrease in cash used in operating activities during the year ended December 31, 2017 compared to the year ended December 31, 2016 was driven primarily by the $21.9 million in deferred revenue related to the License Agreement with Ono and a $10.1 million increase in our accrued expenses and other liabilities balance, offset by an increase in our net loss due to an increase in our operating expenses.

Net cash used in operating activities was $84.4 million during the year ended December 31, 2016 compared to $94.0 million during the year ended December 31, 2015. The $9.6 million decrease in cash used in operating activities during the year ended December 31, 2016 was driven primarily by a decrease in our net loss adjusted for non-cash charges and changes in the components of working capital.

Net Cash Provided by (Used in) Investing Activities

Net cash provided by investing activities decreased by $7.5 million during the year ended December 31, 2017 compared to the year ended December 31, 2016. The decrease was primarily related to a decrease of $43.8 million in proceeds from maturities of investments, offset by a $36.3 million decrease in the purchases of investments.

Net cash provided by investing activities increased $115.4 million during the year ended December 31, 2016 compared to net cash used in investing activities during the year ended December 31, 2015. The increase was primarily related to a decrease of $170.5 million in purchases of investments and a decrease of $1.3 million in purchases of property and equipment, offset by a $56.5 million decrease in the proceeds from maturities of investments.

Net Cash Provided by Financing Activities

Net cash provided by financing activities was $75.7 million during the year ended December 31, 2017 compared to $51.2 million during the year ended December 31, 2016. The cash provided by financing activities for the year ended December 31, 2017 reflects net proceeds of $37.0 million from the sale of common stock as part of the “at-the-market” offering in 2017, net proceeds of $37.9 million from the follow-on offering of common stock in April 2017 and the proceeds from the exercise of stock options and shares issued under our employee stock purchase plan. The cash provided by financing activities for the year ended December 31, 2016 reflects net proceeds of $50.6 million from the sale of common stock as part of the “at-the-market” offering in 2016 and the proceeds from the exercise of stock options and shares issued under our employee stock purchase plan.

Net cash provided by financing activities was $51.2 million during the year ended December 31, 2016 compared to $92.7 million during the year ended December 31, 2015. The cash provided by financing activities for the year ended December 31, 2016 reflects net proceeds of $50.6 million from the sale of common stock as part of the "at-the-market" offering in 2016 and the proceeds from the exercise of stock options and shares issued under our employee stock purchase plan. The cash provided by financing activities for the year ended December 31, 2015 reflects net proceeds of $90.8 million from the sale of common stock as part of a public offering of our common stock in January 2015, net proceeds of $1.5 million from the sale of common stock as part of the "at-the-market" offering in December 2015, and the proceeds from the exercise of stock options and shares issued under our employee stock purchase plan.

Funding requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the clinical trials of, and assuming positive results of our clinical trials and based on regulatory feedback, if and when we seek marketing approval for, selinexor and our other drug candidates. In addition, if we obtain marketing approval for any of our drug candidates, we expect to incur significant commercialization expenses related to drug sales, marketing, manufacturing and distribution 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. 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 future commercialization efforts.

We expect that our cash, cash equivalents and short- and long-term investments as of December 31, 2017, totaling $175.9 million, along with the $10.0 million received from Biogen in 2018, will be sufficient to fund our current operating and capital expenditure plans through at least the first quarter of 2019 while we are establishing the commercial infrastructure for a potential launch of selinexor in the United States. Our future capital requirements will depend on many factors, including:

- 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;
- 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 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, if any, received from commercial sales of our drug candidates, should any of our drug candidates receive marketing approval; and
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

Identifying potential drug candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve drug sales. In addition, our drug

candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that may not be commercially available 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. 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.

Contractual Obligations

As of December 31, 2017, we had the following contractual obligations:

	Payments Due by Period				
Contractual Obligations	**Total**	**Less than 1 Year**	**1 to 3 Years**	**3 to 5 Years**	**More than 5 Years**
			(in thousands)		
Operating lease obligations(1)	$6,775	$1,432	$4,252	$1,091	$—
Purchase obligations(2)	—	—	—	—	—
Total contractual cash obligations	$6,775	$1,432	$4,252	$1,091	$—

(1) Represents future minimum lease payments under our non-cancelable operating lease.

(2) We enter into agreements in the normal course of business with CROs and CMOs for clinical trials and clinical supply manufacturing and with vendors for preclinical research. These contracts generally provide for termination on notice, and therefore are cancelable contracts and not included in this table of contractual obligations and commitments.

Future milestone and royalty payments associated with our agreements have not been included in the above table of contractual obligations as we cannot reasonably estimate if or when they will occur. At this time, no future payments are probable of occurrence.

Multiple Myeloma Research Foundation

In July 2011, we entered into a research agreement with the MMRF for the research and development of small molecule XPO1 inhibitor compounds for the treatment of multiple myeloma. Pursuant to the research agreement, MMRF awarded us a $1.0 million grant, all of which has been paid to us based on our achievement of specified milestones. We own all inventions and other intellectual property that arose or will arise from the conduct of the research program, which we refer to as program inventions and program intellectual property, respectively.

If we, our affiliates, licensees or transferees commercialize products incorporating a program invention or program intellectual property, which we call research program products, we would be obligated to pay to MMRF mid- single-digit royalties as a percentage of worldwide net sales of research program products, including selinexor, sold by us, our affiliates, licensees or transferees. If we out-license rights to a research program product, we are obligated to pay MMRF a percentage of certain payments we receive from our licensee for the grant of such rights. If we sell all or substantially all of our assets to one or more third parties who were not our stockholders on the effective date of the agreement, or if one or more third parties acquire more than fifty percent of our equity and payments are made directly to our stockholders for the sale of their shares of our stock, each of which we call a change of control, we will be obligated to pay to MMRF a percentage of the value we or our shareholders receive in connection with such change of control. The maximum aggregate amount we may be obligated to pay to MMRF for royalties, out-licensing our rights or as a result of a change of control is $6.0 million, of which $2.0 million has been paid through December 31, 2017 in connection with the Ono License Agreement.

While this agreement has expired in accordance with its terms, our payment obligations survive the expiration of the agreement.

Off-Balance Sheet Arrangements

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

Inflation

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

Recently Issued Accounting Pronouncements

Recent accounting pronouncements which may be applicable to us are described in “Note 2. Summary of Significant Accounting Policies” in our Consolidated Financial Statements contained herein in Part II, Item 8.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2017 and 2016, we had cash, cash equivalents, restricted cash and investments of $176.4 million and $175.5 million, respectively. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Due to the short-term maturities of our cash equivalents and the low risk profile of our investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our cash equivalents or investment portfolio.

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

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

Item 8. Financial Statements and Supplementary Data

Our consolidated financial statements, together with the report of our independent registered public accounting firm, appears on pages 116 through 121 of this Annual Report on Form 10-K.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

The Company has established disclosure controls and procedures designed to ensure that information required to be disclosed in the reports that the Company files or submits 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 Executive Vice President, Chief Financial Officer and Treasurer), to allow timely decisions regarding required disclosure.

Our management, under the supervision and with the participation of our Chief Executive Officer and Executive Vice President, Chief Financial Officer and Treasurer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of the end of the period covered by this Annual Report on Form 10-K. Management recognizes that any disclosure controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives. Our disclosure controls and procedures have been designed to provide reasonable assurance of achieving their objectives. Based on such evaluation, our Chief Executive Officer and Executive Vice President, Chief Financial Officer and Treasurer, concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2017.

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, 2017.

Attestation Report of the Registered Public Accounting Firm

This report does not include an attestation report of our independent registered public accounting firm regarding internal control over financial reporting.

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, 2017 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

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 2018 annual meeting of stockholders, pursuant to Regulation 14A of the Exchange Act, which we refer to as our 2018 Proxy Statement. We expect to file our 2018 Proxy Statement with the SEC within 120 days of December 31, 2017.

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 will be included in our 2018 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 2018 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 2018 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 2018 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 2018 Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Financial Statements

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

(a)(2) Financial Statement Schedules

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

(a)(3) Exhibits

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

Item 16. Form 10-K Summary

None.

Report of Independent Registered Public Accounting Firm

To the Stockholders and
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, 2017 and 2016, 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, 2017, 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, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

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

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

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2014.
Boston, Massachusetts
March 15, 2018

Karyopharm Therapeutics Inc.
Consolidated Balance Sheets

(in thousands, except share and per share amounts)

	December 31, 2017	December 31, 2016
ASSETS		
Current assets:		
Cash and cash equivalents	$ 68,997	$ 49,663
Short-term investments	77,472	79,889
Prepaid expenses and other current assets	1,754	2,084
Restricted cash	200	—
Total current assets	148,423	131,636
Property and equipment, net	2,185	2,836
Long-term investments	29,396	45,434
Restricted cash	290	479
Total assets	$ 180,294	$ 180,385
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,665	$ 4,751
Accrued expenses	21,445	11,362
Deferred revenue	21,921	—
Deferred rent	303	280
Other current liabilities	133	83
Total current liabilities	49,467	16,476
Deferred rent, net of current portion	1,363	1,666
Total liabilities	50,830	18,142
Commitments and contingencies (Note 8)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized; none issued and outstanding	—	—
Common stock, $0.0001 par value; 100,000,000 shares authorized; 49,533,150 and 41,887,829 shares issued and outstanding at December 31, 2017 and 2016, respectively	5	4
Additional paid-in capital	625,017	528,617
Accumulated other comprehensive loss	(217)	(274)
Accumulated deficit	(495,341)	(366,104)
Total stockholders' equity	129,464	162,243
Total liabilities and stockholders' equity	$ 180,294	$ 180,385

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,		
	2017	2016	2015
License and other revenue	$ 1,605	$ 154	$ 250
Operating expenses:			
Research and development	107,273	86,938	97,744
General and administrative	24,870	23,948	21,582
Total operating expenses	132,143	110,886	119,326
Loss from operations	(130,538)	(110,732)	(119,076)
Other income (expense):			
Interest income	1,698	1,284	897
Other income (expense)	(81)	10	(2)
Total other income, net	1,617	1,294	895
Loss before income taxes	(128,921)	(109,438)	(118,181)
Provision for income taxes	(63)	(139)	—
Net loss	$ (128,984)	$ (109,577)	$ (118,181)
Net loss per share—basic and diluted	$ (2.81)	$ (2.92)	$ (3.32)
Weighted-average number of common shares outstanding used in net loss per share—basic and diluted	45,899,784	37,523,051	35,619,506

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,		
	2017	2016	2015
Net loss	$ (128,984)	$ (109,577)	$ (118,181)
Other comprehensive income (loss):			
Unrealized gain (loss) on investments	(97)	34	(167)
Foreign currency translation adjustment	154	(26)	(86)
Comprehensive loss	$ (128,927)	$ (109,569)	$ (118,434)

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					
	Shares	Amount	Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity (Deficit)
Balance at December 31, 2014	32,699,380	$ 3	$ 345,166	$ (29)	$ (138,346)	$ 206,794
Vesting of restricted stock	11,410	—	—	—	—	—
Exercise of stock options and shares issued under the employee stock purchase plan	82,661	—	616	—	—	616
Stock-based compensation expense	—	—	17,057	—	—	17,057
Issuance of common stock upon public offering, net of issuance costs of $6,520	2,950,000	—	90,830	—	—	90,830
Issuance of common stock, net of issuance costs of $284	121,314	1	1,501	—	—	1,502
Unrealized loss on investments	—	—	—	(167)	—	(167)
Foreign currency translation adjustment	—	—	—	(86)	—	(86)
Net loss	—	—	—	—	(118,181)	(118,181)
Balance at December 31, 2015	35,864,765	4	455,170	(282)	(256,527)	198,365
Vesting of restricted stock	262,125	—	—	—	—	—
Settlements of restricted stock units for tax withholding obligations	(6,526)	—	(39)	—	—	(39)
Exercise of stock options and shares issued under the employee stock purchase plan	122,383	—	630	—	—	630
Stock-based compensation expense	—	—	22,283	—	—	22,283
Issuance of common stock, net of issuance costs of $1,530	5,645,082	—	50,573	—	—	50,573
Unrealized gain on investments	—	—	—	34	—	34
Foreign currency translation adjustment	—	—	—	(26)	—	(26)
Net loss	—	—	—	—	(109,577)	(109,577)
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 $1,060	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

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,		
	2017	2016	2015
Operating activities			
Net loss	$ (128,984)	$ (109,577)	$ (118,181)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	713	717	634
Net amortization of premiums and discounts on investments	1,187	1,199	1,778
Stock-based compensation expense	20,405	22,283	17,057
Change in operating assets and liabilities:			
Prepaid expenses and other current assets	342	(120)	(55)
Other assets	—	—	500
Accounts payable	909	945	(2,426)
Accrued expenses and other liabilities	10,070	368	5,766
Deferred revenue	21,921	—	—
Deferred rent	(280)	(206)	213
Cash received related to tenant lease incentives	—	—	685
Net cash used in operating activities	(73,717)	(84,391)	(94,029)
Investing activities			
Purchases of property and equipment	(62)	(70)	(1,416)
Increase in restricted cash	—	—	(82)
Proceeds from maturities of investments	115,544	159,365	215,867
Purchases of investments	(98,374)	(134,700)	(305,192)
Net cash provided by (used in) investing activities	17,108	24,595	(90,823)
Financing activities			
Proceeds from issuance of common stock, net of issuance costs	74,885	50,573	92,084
Proceeds from the exercise of stock options and shares issued under employee stock purchase plan	858	630	616
Settlements of restricted stock units for tax withholding obligations	—	(39)	—
Net cash provided by financing activities	75,743	51,164	92,700
Effect of exchange rate on cash	200	(63)	(99)
Net increase (decrease) in cash and cash equivalents	19,334	(8,695)	(92,251)
Cash and cash equivalents, beginning of period	49,663	58,358	150,609
Cash and cash equivalents, end of period	$ 68,997	$ 49,663	$ 58,358
Supplemental disclosure of non-cash investing and financing activities:			
Deferred financing costs included in accounts payable and accrued expenses	$ —	$ —	$ 26

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

Karyopharm Therapeutics Inc.
Notes to Consolidated Financial Statements

(in thousands, except share and per share amounts)

1. Organization and Operations

The Company

Karyopharm Therapeutics Inc. (the "Company") is a clinical stage pharmaceutical company that seeks to discover, develop, and commercialize drugs to treat cancer and certain other major diseases. It was incorporated in Delaware on December 22, 2008 and has a principal place of business in Newton, Massachusetts.

The Company's operations to date have consisted primarily of raising capital, product research and development, and initial market development.

The Company has not generated any revenue from product sales and is subject to a number of risks similar to those of other clinical stage life science companies, including rapid technology change, regulatory approval of products, uncertainty of market acceptance of products, compliance with government regulations, protection of proprietary technology, dependence on key individuals, competition from other companies, the need for development of commercially viable products, and the need to obtain adequate additional financing to fund the development of its product candidates.

The Company has generated an accumulated deficit of $495,341 since inception. The Company has financed its operations to date primarily through private placements of its preferred stock, proceeds from its initial public offering and follow-on offerings of common stock and cash generated from its business development activities. The Company has not completed development of any product candidate and has devoted substantially all of its financial resources and efforts to research and development, including preclinical and clinical development. The Company expects to continue to incur significant expenses and increasing operating losses for at least the foreseeable future. The Company believes its cash, cash equivalents and investments as of December 31, 2017, along with the $10,000 received from Biogen MA Inc. in 2018 as discussed in Note 13, will be sufficient to allow the Company to fund its current operating and capital expenditure plans through at least the first quarter of 2019.

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. The Company views its operations and manages its 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 the Company's revenues are derived in the United States. All material long-lived assets of the Company 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.

On an ongoing basis, the Company's management evaluates its estimates, including estimates related to clinical trial accruals, stock-based compensation expense, and reported amounts of expenses during the reported period. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Although the Company regularly assesses 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, 2017 include the accounts of the Company, the accounts of Karyopharm Securities Corp. ("KPSC", a wholly-owned Massachusetts corporation of the Company incorporated in December 2013), the accounts of Karyopharm Europe GmbH (a wholly-owned German Limited Liability Company, incorporated in September 2014), and the accounts of Karyopharm Therapeutics (Bermuda) Ltd. (a limited liability company, registered in Bermuda in March 2015).

Cash and Cash Equivalents

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. The Company considers all highly liquid investments with maturities of three months or less from the date of purchase to be cash equivalents. The Company does not hold any money market funds with significant liquidity restrictions that would be required to be excluded from cash equivalents.

Investments

The Company determines the appropriate classification of its investments in debt securities at the time of purchase. All of the Company's 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 on the Company's Consolidated Balance Sheets, 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 the Company to credit risk consist primarily of cash, cash equivalents and investment securities. The Company holds these investments in highly rated financial institutions, and, by policy, limits the amounts of credit exposure to any one financial institution. These amounts at times may exceed federally insured limits. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to any significant credit risk on these funds. The Company has 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 in the consolidated financial statements at amounts that approximate fair value at December 31, 2017 and 2016.

The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. The fair value hierarchy

prioritizes valuation inputs based on the observable nature of those inputs. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The hierarchy defines three levels of valuation inputs:

Level 1 inputs	Quoted prices in active markets for identical assets or liabilities
Level 2 inputs	Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly
Level 3 inputs	Unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability

The Company's cash equivalents are composed of money market funds. The Company measures 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. The Company estimates 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. The Company validates the prices provided by its third-party pricing sources by understanding the models used, obtaining market values from other pricing sources and analyzing pricing data in certain instances.

The following table presents information about the Company's financial assets that have been measured at fair value at December 31, 2017 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	$ 41,805	$ 41,805	$ —	$ —
Investments:				
Current:				
Corporate debt securities	66,253	—	66,253	—
Commercial paper	6,720	—	6,720	—
Certificates of deposit	2,500	—	2,500	—
U.S. government and agency securities	1,999	—	1,999	—
Non-current:				
Corporate debt securities (one to two year maturity)	26,916	—	26,916	—
U.S. government securities and agency securities	2,480	—	2,480	—
	$148,673	$ 41,805	$ 106,868	$ —

The following table presents information about the Company's financial assets that have been measured at fair value at December 31, 2016 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	$ 37,916	$ 37,916	$ —	$ —
Investments:				
Current:				
Corporate debt securities	52,722	—	52,722	—
Commercial paper	24,668	—	24,668	—
U.S. government and agency securities	2,499	—	2,499	—
Non-current:				
Corporate debt securities (one to two year maturity)	43,435	—	43,435	—
U.S. government securities	1,999	—	1,999	—
	$163,239	$ 37,916	$ 125,323	$ —

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

The Company reviews the carrying values of its 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. The Company has 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 the Company's operating leases. Rent escalation represents the difference between actual operating lease payments due and straight-line rent expense, which is recorded by the Company over the term of the lease. Tenant improvement allowances and other incentives are recorded as deferred rent and amortized as a reduction of periodic rent expense, over the term of the applicable lease.

Revenue Recognition

The Company recognizes revenue when persuasive evidence of an arrangement exists; services have been performed or products have been delivered; the fee is fixed or determinable; and collection is reasonably assured.

The Company generates revenue from collaboration and license agreements with pharmaceutical companies for the development and commercialization of certain of its product candidates. Collaboration and license agreements may include non-refundable upfront payments, reimbursement of research and development services and costs, payments based upon the achievement of defined milestones, license fees and profit share and/or royalties on sales of product candidates if they are successfully approved and commercialized. The Company's performance obligations under the collaborations may include the transfer of intellectual property rights in the form of licenses, obligations to provide research and development services and participation on certain committees with the licensors. The Company makes judgments that affect the periods over which it recognizes revenue.

The Company evaluates multiple element agreements under the Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Revenue Recognition (Topic 605). When evaluating multiple element arrangements under Topic 605, the Company identifies the deliverables included within the agreement and determines whether the deliverables under the arrangement represent separate units of accounting. Deliverables under the arrangement are a separate unit of accounting if (i) the delivered item has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item and delivery or performance of the undelivered items are considered probable and substantially within the Company's control. This evaluation requires subjective determinations and requires management to make judgments about the individual deliverables and whether such deliverables are separable from the other aspects of the contractual relationship. In determining the units of accounting, management evaluates certain criteria, including whether the deliverables have standalone value, based on the consideration of the relevant facts and circumstances for each arrangement. The Company considers whether the licensor can use the license or other deliverables for their intended purpose without the receipt of the remaining elements, and whether the value of the deliverable is dependent on the undelivered items and whether there are other vendors that can provide the undelivered items.

Arrangement consideration generally includes up-front license fees. The Company determines how to allocate arrangement consideration to identified units of accounting based on the selling price hierarchy provided under the relevant guidance. The Company determines the estimated selling price for deliverables using vendor-specific objective evidence ("VSOE") of selling price, if available, third-party evidence ("TPE"), if VSOE is not available, or best estimate of selling price ("BESP"), if neither VSOE nor TPE is available. Determining the BESP for a deliverable requires significant judgment. The estimated selling prices may be based on similar license arrangements, the nature of the research and development services to be performed and market rates for similar services.

As described below in *Recently Issued Accounting Pronouncements*, the Company adopted ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)* on January 1, 2018.

Up-Front License Fees

Up-front payments received in connection with licenses of the Company's technology rights are deferred if facts and circumstances dictate that the license does not have stand-alone value. When management believes the license to its intellectual property does not have stand-alone value from the other deliverables to be provided in the arrangement, it is combined with other deliverables and the revenue of the combined unit of accounting is recorded based on the method appropriate for the last delivered item.

Milestones

At the inception of each arrangement that includes milestone payments, the Company evaluates whether each milestone is substantive, in accordance with Accounting Standards Update ("ASU") No. 2010-17, *Revenue Recognition—Milestone Method.* A milestone is defined as an event that can only be achieved based on the Company's performance and there is substantive uncertainty about whether the event will be achieved at the

inception of the arrangement. Events that are contingent only on the passage of time or only on counterparty performance are not considered milestones under this accounting guidance. This evaluation includes an assessment of whether (a) the consideration is commensurate with either (1) the Company's performance to achieve the milestone, or (2) the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the Company's performance to achieve the milestone, (b) the consideration relates solely to past performance, (c) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement and (d) the milestone fee is refundable or adjusts based on future performance or non-performance. The Company evaluates factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the respective milestone, the level of effort and investment required to achieve the respective milestone and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement in making this assessment. Payments that are contingent upon the achievement of a substantive milestone are recognized in their entirety in the period in which the milestone is achieved, assuming all other revenue recognition criteria are met. At December 31, 2017, the Company could receive up to approximately $96,250 in milestone payments if certain clinical, regulatory and development goals are achieved and up to approximately $117,700 in milestone payments if certain sales milestones are achieved.

Sales-based and commercial milestones are accounted for as royalties and are recorded as revenue upon achievement of the milestone, assuming all other revenue recognition criteria are met.

Grant Revenue

During 2016, the Company was awarded a government grant from the National Institute of Health. This grant provides the Company with cost reimbursement up to $225 for certain types of expenditures in return for research and development activities over a period of one year. Grant revenues are recognized in the period during which the related costs are incurred, provided that the conditions under which the costs submitted or to be submitted for reimbursement have been met and the Company has only perfunctory obligations outstanding. During the years ended December 31, 2017 and December 31, 2016, the Company earned $71 and $154, respectively, in revenue under this grant. There are no future milestones to be met under this grant.

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 the Company by its 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 the Company's subsidiary in Germany is the Euro. Foreign currency transaction gains and losses are recorded in the consolidated statement of operations. Net foreign exchange gains (losses) of $(62), $10 and $(2) were recorded in other income (expense) for the years ended December 31, 2017, 2016 and 2015, respectively.

Income Taxes

The Company uses 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. The Company provides 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. The Company has evaluated available evidence and concluded that the Company may not realize the benefit of its deferred tax assets; therefore, a valuation allowance has been established for the full amount of the deferred tax assets. The Company recognizes interest and/or penalties related to income tax matters in income tax expense. The Company's foreign tax provision pertains to foreign income taxes due at its German subsidiary which operates on a cost plus profit margin basis.

On December 22, 2017, the Tax Cuts and Jobs Act of 2017 was signed into law, which resulted in significant changes to the U.S. corporate income tax system. For additional details regarding this act, see Note 12, "Income Taxes".

Accounting for Stock-Based Compensation

The Company accounts for its 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, including grants of employee stock options, restricted stock and restricted stock units, as well as modifications to existing stock options and shares issued under the Company's employee stock purchase plan (ESPP), to be recognized in the consolidated statements of operations based on their fair values. The Company uses the Black-Scholes option pricing model to determine the fair value of options granted.

Consistent with the guidance in FASB ASC Topic 505-50, *Equity-Based Payments to Non-Employees*, the fair value of each non-employee stock option is estimated at the date of grant using the Black-Scholes option pricing model with assumptions generally consistent with those used for employee stock options, with the exception of expected term, which is over the contractual life.

Compensation expense related to awards to employees 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. Stock-based compensation expense for awards granted to non-employees is adjusted as the award vests to reflect the current fair value of such awards, and is recognized using an accelerated attribution model. As described below, forfeitures are recognized as they occur.

For performance-based restricted stock, at each reporting period the Company assesses the probability that the performance condition(s) will be achieved. The Company uses the accelerated attribution method to expense the awards over the implicit service period based on the probability of achieving the performance conditions. The Company estimates the implicit service period based on its best estimate of the period over which an award's vesting condition(s) will be achieved. The Company reviews and evaluates these estimates on a quarterly basis and will recognize any remaining unrecognized compensation expense as of the date of an estimate revision over the revised remaining implicit service period.

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. The Company's 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, 2017, 2016 and 2015 (in common stock equivalent shares):

	December 31,		
	2017	2016	2015
Outstanding stock options	7,019,083	5,574,179	4,443,317
Unvested restricted stock units	253,100	214,300	508,800

Recently Issued Accounting Pronouncements

In August 2016, the FASB issued ASU 2016-15, *Classification of Certain Cash Receipts and Cash Payments* ("ASU 2016-15"). ASU 2016-15 addresses eight specific cash flow issues with the objective of reducing the existing diversity in practice. ASU 2016-15 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2017. Early adoption is permitted. The Company does not expect the adoption of ASU 2016-05 to have a material impact on its results of operations, financial position or cash flows.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash*. The new standard requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The standard is effective for annual reporting periods beginning after December 15, 2017, and interim periods within annual periods beginning after December 15, 2017. Early adoption is permitted. The Company has evaluated this standard and does not believe it will have a material impact on the Company's consolidated financial statements.

In October 2016, the FASB issued ASU No. 2016-16, *Accounting for Income Taxes: Intra-Entity Asset Transfers of Assets Other than Inventory (Topic 740)*. Topic 740 eliminates the ability to defer the tax expense related to intra-entity asset transfers other than inventory. Under the new standard, entities should recognize the income tax consequences on an intra-entity transfer of an asset other than inventory when the transfer occurs. Topic 740 is effective for fiscal periods beginning after December 15, 2018. Early adoption is permitted. The Company is evaluating the potential impact that the adoption of this standard may have on the Company's financial position or results of operation.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)*. The new standard requires that all lessees recognize the assets and liabilities that arise from leases on the balance sheet and disclose qualitative and quantitative information about its leasing arrangements. The new standard will be effective for the Company on January 1, 2019. The Company is in process of evaluating this guidance and determining the potential impact on its consolidated financial statements; however, it anticipates that the new standard will result in the Company recording additional assets and corresponding liabilities on its consolidated balance sheets. The Company expects that the implementation of the new standard will have an impact on its internal controls, systems and processes.

In August 2015, the FASB issued ASU 2015-14, *Revenue from Contracts with Customers (Topic 606): Deferral of Effective Date*, which defers the effective date of ASU 2014-09, *Revenue from Contracts with*

Customers (Topic 606), for all entities by one year. ASU 2014-09 and subsequent amendments have been codified as ASC 606, *Revenue from Contracts with Customers*. The new standard is now effective for public companies for annual reporting periods beginning after December 15, 2017, including interim periods within those reporting periods. ASC 606 outlines a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most of the current revenue recognition guidance, including industry-specific guidance. In addition, ASC 606 provides guidance on accounting for certain revenue-related costs including, but not limited to, when to capitalize costs associated with obtaining and fulfilling a contract. ASC 606 provides companies with two implementation methods. Companies can choose to apply the standard retrospectively to each prior reporting period presented (full retrospective application) or retrospectively with the cumulative effect of initially applying the standard as an adjustment to the opening balance of retained earnings of the annual reporting period that includes the date of initial application (modified retrospective application).

The Company adopted ASC 606 effective January 1, 2018 using the modified retrospective method. The Company is in the process of finalizing the impact of ASC 606 on its revenue arrangements with Anivive Lifesciences, Inc. and Ono Pharmaceutical Co., both as described in Note 7, Collaboration and License Agreements. The Company does not believe the adoption of the new standard will have a material impact on its consolidated financial statements. The modified retrospective method applies the guidance retrospectively only to the most current period presented in the financial statements, recognizing the cumulative effect of initially applying the standard as an adjustment to the opening balance of accumulated deficit at the date of initial application. *Recently Adopted Accounting Standards*

In March 2016, the FASB issued ASU No. 2016-09, *Compensation—Stock Compensation (Topic 718)*. The new standard identifies areas for simplification involving several aspects of accounting for share-based payment transactions, including income tax consequences, classification of awards as either equity or liabilities, an option to recognize gross stock compensation expense with actual forfeitures recognized as they occur, as well as certain classifications on the statement of cash flows. The new standard also provides for companies to make a policy election on accounting for forfeitures. The Company adopted the new standard on January 1, 2017 and has elected to account for forfeitures as they occur. The change was applied on a modified retrospective basis with a cumulative effect adjustment to increase additional paid-in capital and charge accumulated deficit by $253, as of January 1, 2017. In addition, upon adoption of the new standard, the Company has additional deferred tax assets related to tax deductions from excess tax benefits related to the exercise of stock options. As a result, the deferred tax assets associated with net operating losses increased by $1,844 in the first quarter of 2017. The amounts are offset by a corresponding increase in the valuation allowance; therefore, there is no net effect on the Company's results of operations for the year ended December 31, 2017.

3. Property and Equipment, net

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

	Estimated Useful Life Years	December 31, 2017	December 31, 2016
Laboratory equipment	4	$ 593	$ 538
Furniture and fixtures	5	381	381
Office and computer equipment	3	378	371
Leasehold improvements	Lesser of useful life or lease term	3,391	3,391
		4,743	4,681
Less accumulated depreciation and amortization		(2,558)	(1,845)
		$ 2,185	$ 2,836

Depreciation and amortization expense recorded for the years ended December 31, 2017, 2016, and 2015 was $713, $717 and $634, respectively.

4. Investments

The following table summarizes the Company's investments as of December 31, 2017 (in thousands):

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Loss	Fair Value
Current:				
Corporate debt securities	$ 66,384	$ —	$ (131)	$ 66,253
Commercial paper	6,719	1	—	6,720
Certificates of deposit	2,500	—	—	2,500
U.S. government and agency securities	2,000	—	(1)	1,999
Non-current:				
Corporate debt securities (one to two year maturity)	27,018	2	(104)	26,916
U.S. government and agency securities	2,500	—	(20)	2,480
	$ 107,121	$ 3	$ (256)	$106,868

The following table summarizes the Company's investments as of December 31, 2016 (in thousands):

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Loss	Fair Value
Current:				
Corporate debt securities	$ 52,762	$ 5	$ (45)	$ 52,722
Commercial paper	24,670	5	(7)	24,668
U.S. government and agency securities	2,500	—	(1)	2,499
Non-current:				
Corporate debt securities (one to two year maturity)	43,546	29	(140)	43,435
U.S. government and agency securities	2,000	—	(1)	1,999
	$ 125,478	$ 39	$ (194)	$125,323

At December 31, 2017 and December 31, 2016, the Company held 54 and 58 debt securities, respectively, that were in an unrealized loss position for less than one year. The aggregate fair value of debt securities in unrealized loss positions at December 31, 2017 and December 31, 2016 was $96,623 and $95,949, respectively. There were no individual securities that were in a significant unrealized loss position or that had been in an unrealized loss position for greater than one year as of December 31, 2017 or December 31, 2016.

The Company reviews 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 the Company has experienced a credit loss or has the intent to sell the investment or if it is more likely than not that the Company 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 the Company's investment policy, the severity and the duration of the impairment and changes in value subsequent to the end of the period.

5. Accrued Expenses

Accrued expenses consisted of the following (in thousands):

	December 31,	
	2017	2016
Research and development costs	$16,198	$ 6,855
Payroll and employee-related costs	3,982	3,476
Professional fees	972	480
Other	293	551
	$21,445	$11,362

6. Related Party Transactions

The Company incurred expenses for consulting and contract research services with certain related parties, including a family member of management, a board member and a private diagnostics company, of which three members of the Company's Board of Directors, including the Company's CEO, were also members of the private company's Board of Directors. The Company paid consulting services of $101 for the year ended December 31, 2017 and consulting and histopathology services of $269 and $456 for the years ended December 31, 2016, and 2015, respectively, to these related parties. At December 31, 2017 and 2016, there was $34 and $0, respectively, included in accounts payable and accrued expenses due to related parties.

7. Stockholders' Equity

Controlled Equity Offering Sales Agreement

On December 7, 2015, the Company entered into a Controlled Equity Offering Sales Agreement (as amended from time to time, the "Sales Agreement"), with Cantor Fitzgerald & Co., as sales agent ("Cantor"), pursuant to which the Company issued and sold through Cantor, shares of the Company's common stock (the "Shares"), up to an aggregate offering price of $50,000. On November 7, 2016, the Company entered into an amendment to the Sales Agreement pursuant to which it issued and sold Shares having an additional aggregate offering price of up to $50,000. On December 1, 2017, the Company entered into a second amendment to the Sales Agreement that provides that it may issue and sell Shares having an additional aggregate offering price of up to $75,000.

Under the Sales Agreement, Cantor may sell the Shares 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"), including sales made directly on The Nasdaq Global Select Market, on any other existing trading market for the Shares or to or through a market maker. In addition, under the Sales Agreement, Cantor may sell the Shares by any other method permitted by law, including in privately negotiated transactions.

The Company is not obligated to make any sales of the Shares under the Sales Agreement. The Company or Cantor may suspend or terminate the offering of Shares upon notice to the other party and subject to other conditions. The Company will pay Cantor a commission of up to 3.0% of the gross proceeds from the sale of the Shares pursuant to the Sales Agreement and has agreed to provide Cantor with customary indemnification and contribution rights.

During 2017, the Company sold an aggregate of 3,405,763 Shares under the Sales Agreement for net proceeds of approximately $36,978.

During 2016, the Company sold an aggregate of 5,645,082 Shares under the Sales Agreement for net proceeds of approximately $50,573.

During 2015, the Company sold an aggregate of 121,314 Shares under the Sales Agreement for net proceeds of approximately $1,502.

Common Stock

In April 2017, the Company completed an underwritten offering of 3,902,439 shares of its common stock at a public offering price of $10.25 per share. The net proceeds received by the Company were $37,907 after deducting the underwriting discount and offering expenses payable by the Company.

In January 2015, the Company completed an underwritten offering of 2,950,000 shares of its common stock at a public offering price of $33.00 per share. The net proceeds received by the Company were $90,830 after deducting the underwriting discount and offering expenses payable by the Company.

As of December 31, 2017, 2016 and 2015, the Company did not have any preferred stock issued or outstanding.

8. Commitments and Contingencies

Operating Leases

In March 2014, the Company entered into an operating lease for approximately 29,933 square feet of office and research space in Newton, Massachusetts. The Company uses the leased premises as its corporate headquarters and for research and development purposes. The lease was amended on December 31, 2014 by extending the lease term of the lease from November 30, 2021 to approximately September 30, 2022. The amendment to the lease also provided for the expansion of the premises leased by the Company by approximately 16,234 square feet. The Company may extend the lease term for one additional five year period. The Company has agreed to pay pro rata increases in operating expenses and property taxes. The Company is recording rent expense on a straight-line basis through the end of the lease term, inclusive of the period in which there are no scheduled rent payments. The Company has recorded deferred rent on the consolidated balance sheet at December 31, 2017 and December 31, 2016, accordingly. The lease provides the Company with an allowance for improvements of $1,616, all of which was incurred in the first quarter of 2015 and was deemed normal tenant improvements. Therefore, the amounts were recorded as a leasehold improvement and deferred rent and are being recorded as a reduction to rent expense ratably over the lease term. The Company has provided a security deposit in the form of a cash-collateralized letter of credit in the amount of $400, which amount was reduced to $200 in January 2018. The amount is classified as restricted cash on the consolidated balance sheet.

In November 2014, the Company signed a five-year operating lease agreement in Munich, Germany for approximately 3,681 square feet of office space. The lease is for the period from February 2015 through January 2020. Pursuant to the lease agreement, the Company was obligated to make aggregate rent payments of €374, (approximately US$449) through January 31, 2020. The Company is recording rent expense on a straight-line basis through the end of the lease term, inclusive of the period in which there are no scheduled rent payments.

As of December 31, 2017, the minimum future rent payments under the lease agreements are as follows (in thousands):

2018	$ 1,432
2019	1,455
2020	1,390
2021	1,407
2022	1,091
Thereafter	—
Total future minimum lease payments	$ 6,775

The Company recorded rent expense totaling $1,198, $1,150 and $1,033 for the years ended December 31, 2017, 2016, and 2015, respectively.

Research Agreements

In July 2011 and September 2013, the Company entered into research agreements in which the Company received payments upon the achievement of certain milestones. The agreements require the Company to pay royalties on product sales and on a portion of any other sublicense income. The Company made payments of $2,221 in connection with these agreements in the year ended December 31, 2017 and recorded research and development expense, accordingly. No royalty payments on product sales have been made to date.

Litigation

From time to time the Company may face legal claims or actions in the normal course of business. The Company is not currently a party to any material litigation and, accordingly, does not have amounts recorded for any litigation-related matters.

9. Collaboration and License Agreements

Ono License Agreement

Effective October 11, 2017 (the "Effective Date"), the Company entered into a license agreement (the "Agreement") with Ono Pharmaceutical Co., Ltd., a corporation organized and existing under the laws of Japan ("Ono"), pursuant to which the Company granted Ono exclusive rights to develop and commercialize, at its own cost, selinexor (KPT-330), the Company's lead, novel, oral Selective Inhibitor of Nuclear Export (SINE™) compound, as well as KPT-8602, the Company's second-generation oral SINE™ compound, for the diagnosis, treatment and/or prevention of all human oncology indications (the "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"). Pursuant to the terms of the Agreement, the Company received an upfront payment of ¥2.5 billion (US$21,916 on the date received), and could receive up to ¥10.15 billion (approximately US$90,500 at the exchange rate as of the Effective Date) in milestone payments if certain development goals are achieved and up to ¥9.0 billion (approximately US$80,200 at the exchange rate as of the 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 KPT-8602 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 "Manufacturing Election"), the Company will grant to Ono non-exclusive rights to manufacture selinexor, KPT-8602 and products containing such compounds in or outside of the Ono Territory solely for development and commercialization in the Field in the Ono Territory.

As part of the Agreement, Ono will also have the right to participate in global clinical studies of selinexor and KPT-8602, 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 KPT-8602 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 KPT-8602 in the Field in the Ono Territory at its own cost and expense.

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

The 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 Agreement may be terminated earlier by (i) either party for breach of the 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) the Company in the event Ono challenges or assists with a challenge to certain of the Company's patent rights.

In accordance with ASC 605, the Company identified the deliverables at the inception of the Agreement. The significant deliverables were determined to include the license and transfer of technological know-how, as well as delivery of an agreed amount of drug substance. The Company determined that the license and transfer of technological know-how did not have stand-alone value separate and apart from the drug substance because (1) there are no other vendors selling the drug substance (2) Ono is unable to use the license and technological know-how for its intended purpose without the drug substance. As such, the Company determined there is one unit of accounting. The total consideration related to the upfront payment of $21,916, was allocated to the single unit of accounting and will be recognized as revenue once the drug substance is delivered, which is the final item to be delivered in the combined unit of accounting and is currently expected in 2018. As of December 31, 2017, the $21,916 upfront payment was included in deferred revenue and is classified as a current liability in the consolidated balance sheet.

MMRF Research Agreement

The Company is a party to a research agreement with the Multiple Myeloma Research Foundation ("MMRF"). Under this research agreement, the Company is obligated to make certain payments to MMRF, including if the Company out-licenses selinexor. The terms of this research agreement do not apply to KPT-8602. In connection with the transactions contemplated under the Agreement, the Company paid to MMRF approximately ¥225 million (US$1,972) of the upfront cash payment from Ono, and it will be obligated to pay a percentage of any milestone payments from Ono and a mid-single-digit percentage of any royalty payments from Ono. The maximum aggregate amount the Company may be obligated to pay to MMRF under the research agreement is $6,000.

Anivive License Agreement

On April 28, 2017, the Company entered into a license agreement with Anivive Lifesciences, Inc. ("Anivive"), a biopharmaceutical company engaged in the research, development and commercialization of animal health medicines, pursuant to which the Company has granted Anivive an exclusive, worldwide license to develop and commercialize verdinexor (KPT-335) for the treatment of cancer in companion animals (the "Anivive Agreement"). Pursuant to the terms of the Anivive Agreement, the Company received an upfront payment of $1,000. In addition, the Company will be eligible to receive potential future technology transfer and clinical, regulatory and commercial development milestone payments totaling up to $43,500, as well as a low double digit royalty based on Anivive's future net sales of verdinexor following commercialization. The potential future milestone payments are composed of $250 for completion of the technology transfer, $5,750 based on achievement of clinical and regulatory milestone events and $37,500 based on achievement of sales milestone events.

In accordance with ASC 605, the Company identified the deliverables at the inception of the Anivive Agreement. The significant deliverables were determined to include the license and the Company's responsibility to transfer the technology package relating to verdinexor. The Company determined that the license does not have stand-alone value separate and apart from the transfer of the verdinexor technology package to Anivive because (1) there are no other vendors selling similar licenses on a stand-alone basis and (2) Anivive is unable to use the license for its intended purpose without the technology transfer. As such, the Company determined that there is one unit of accounting. The total consideration of $1,250, including the $1,000 upfront payment and a $250 payment for completion of the technology transfer, was allocated to the single unit of accounting and was

recognized as revenue when the technology transfer was completed, which was the final item to be delivered in the unit of accounting. The technology transfer was completed in October 2017 and the $1,250 was recognized as revenue accordingly.

10. Stock-based Compensation

During 2010, the Company established the 2010 Stock Incentive Plan (the "Plan" or the "2010 Plan"). Under the terms of the Plan, options were granted to employees, officers, directors, consultants and advisors of the Company. 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. The Company 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. The Company will grant no further stock options or other awards under the 2010 Plan.

In October 2013, the Company's board of directors adopted and the Company's 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 the Company 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 2016 and 2017 the number of shares available for issuance under the 2013 Plan was increased by 1,434,490 and 1,675,513 shares of common stock, respectively. As of December 31, 2017, the Company had 726,707 shares available for issuance.

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

	Year Ended December 31,		
	2017	2016	2015
Research and development	$11,208	$12,142	$ 8,368
General and administrative	9,197	10,141	8,689
Total	$20,405	$22,283	$17,057

Stock Options

Total expense related to employee and non-employee stock options for the years ended December 31, 2017, 2016 and 2015 was $16,739, $17,867 and $16,094, respectively.

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

	Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (year)	Aggregate Intrinsic Value
Options outstanding at December 31, 2016	5,574,179	$ 16.55	7.7	$ 12,178
Granted	2,608,200	10.19		
Exercised	(97,041)	4.67		
Forfeited	(1,066,254)	20.38		
Options outstanding at December 31, 2017	7,019,083	$ 13.77	7.4	$ 11,897
Options exercisable at December 31, 2017	3,715,329	$ 15.70	6.1	$ 10,153

The total intrinsic value of stock options exercised for the years ended December 31, 2017, 2016 and 2015 was $446, $347 and $1,248, 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,		
	2017	2016	2015
Volatility	79%-85%	79%-85%	79%-88%
Expected term (in years)	5.5-9.6	5.5-9.8	5.0-9.9
Risk-free interest rate	1.76%-2.29%	1.07%-2.09%	1.45%-2.33%
Dividend	0%	0%	0%

The Company uses 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 it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term for options granted to employees and utilizes the contractual term for options granted to non-employees. The expected term is applied to the stock option grant group as a whole, as the Company does not expect substantially different exercise or post-vesting termination behavior among its employee population. The expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to the Company, including early stage of product development and therapeutic focus. For these analyses, the Company selects companies with comparable characteristics to theirs 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. As described in Note 2, the Company adopted Topic 718 as of January 1, 2017 and now accounts for forfeitures as they occur. Management, prior to adoption, estimated expected forfeitures based on historical data from the Company and recognized compensation costs only for those equity awards expected to vest.

Using the Black-Scholes option-pricing model, the weighted-average grant date fair values of options granted during the years ended December 31, 2017, 2016 and 2015 was $7.22, $5.00 and $18.67 per share, respectively.

At December 31, 2017, the total unrecognized compensation related to unvested employee and non-employee stock option awards granted under the 2010 Plan and 2013 Plan was $22,021, which the Company expects to recognize over a weighted-average period of approximately 2.3 years.

Restricted Stock

To date, the Company has granted 1,958,210 shares of restricted stock outside of the 2010 Plan and the 2013 Plan and 45,454 shares of restricted stock under the 2010 Plan. The total expense related to employee and non-employee restricted stock for the years ended December 31, 2017, 2016 and 2015 was $0, $0 and $111, respectively.

As of December 31, 2017, there was no unrecognized compensation cost related to employee and non-employee unvested restricted stock.

Restricted Stock Units

A restricted stock unit ("RSU") represents the right to receive one share of the Company's common stock upon vesting of the RSU. The fair value of each RSU is based on the closing price of the Company's common stock on the date of grant. In November 2015, the Company granted RSUs with service conditions that vest in two equal annual installments provided that the employee remains employed with the Company ("Time-Based RSUs"). During the year ended December 31, 2017, the Company granted performance-based RSUs, which vest upon the achievement of certain performance goals subject to the employee's continued employment ("Performance-Based RSUs"). In the event the performance goals are not achieved, none of the Performance-Based RSUs will vest. The grant date fair value of the outstanding Performance-Based RSUs was $2,400 and will be recognized on an accelerated attribution basis when the Performance-Based RSUs are deemed probable of achievement to the date the awards vest. During the year ended December 31, 2017, the Company recognized $830 of stock-based compensation expense related to the Performance-Based RSUs, as certain of the Performance-Based RSUs were deemed probable of achievement as of December 31, 2017.

As of December 31, 2017, the Company has granted 855,600 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, 2017 and 2016, respectively:

	Number of Shares Underlying RSUs	Weighted-Average Grant Date Fair Value
Unvested at December 31, 2015	508,800	$ 17.91
Granted	25,000	8.06
Forfeited	(57,375)	17.91
Vested	(262,125)	16.97
Unvested at December 31, 2016	214,300	$ 17.91
Granted	318,800	10.29
Forfeited	(97,504)	12.81
Vested	(182,496)	17.19
Unvested at December 31, 2017	253,100	$ 10.27

The total stock-based compensation expense related to RSUs, including Performance-Based RSUs, for the years ended December 31, 2017, 2016 and 2015 was $3,447, $4,212 and $660, respectively.

As of December 31, 2017, there was $252 of unrecognized compensation costs related to unvested Time-Based RSUs, which are expected to be recognized over a weighted average period of 1.6 years.

Employee Stock Purchase Plan

The Company has an Employee Stock Purchase Plan ("ESPP") that permits eligible employees to enroll in six-month offering periods. Participants may purchase shares of the Company's 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, the Company's 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 the Company's common stock, 1% of the number of outstanding shares on such date, or an amount determined by the board of directors.

During the years ended December 31, 2017, 2016 and 2015, $404, $340 and $352, respectively, was withheld from employees, on an after-tax basis, in order to purchase 57,582, 46,815 and 25,421 shares of the Company's common stock, respectively. For the years ended December 31, 2017, 2016 and 2015, the Company recorded stock-based compensation expense of $219, $204 and $192, respectively. As of December 31, 2017, 433,511 shares of Company's common stock remained available for issuance under the ESPP. As of December 31, 2017, there was $93 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,	
	2017	2016
Volatility	48.2%-77.8%	77.8%-95.5%
Expected term (in years)	0.5	0.5
Risk-free interest rate	0.5%-1.30%	0.27%-0.50%
Dividend	0%	0%

11. 401(k) Plan

The Company has 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, the Company adopted a Safe Harbor Plan that provides a Company match up to 4% of salary. The Company contributed a match of $572, $491 and $366 to the 401(k) Plan for the years ended December 31, 2017, 2016 and 2015, respectively.

12. 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, the Company was 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. As a result, the Company recorded a reduction to its deferred tax asset for $42,763 and a corresponding reduction to its valuation allowance. There was no impact to the Company's income statement due to the reduction in the U.S. corporate tax rate. The Company's preliminary estimate of the TCJA and the remeasurement of the Company's deferred tax assets and liabilities is subject to the finalization of management's analysis related to certain matters, such as developing interpretations of the provisions of the TCJA, changes to certain estimates and the filing of the Company's tax returns. U.S. Treasury regulations, administrative interpretations or court decisions interpreting the TJCA may require further adjustments and changes in the Company's estimates. The final determination of the TCJA and the remeasurement of the Company's deferred assets and liabilities will be completed as additional information becomes available, but no later than one year from the enactment of the TCJA.

Income Taxes

For the year ended December 31, 2017 and 2016, the Company recorded an income tax expense of $63 and $139 for its operations in Germany. For the year ended December 31, 2015, the income tax expense was not material and it was recorded in income (loss) before income taxes. The Company's foreign tax provision pertains to foreign income taxes due at its German subsidiary which operates on a cost plus profit margin.

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

	Year Ended December 31,		
	2017	2016	2015
Foreign	$ (35,680)	$ (26,928)	$ (21,409)
U.S.	(93,241)	(82,510)	(96,676)
Totals	$ (128,921)	$ (109,438)	$ (118,085)

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 the Company's deferred tax assets are comprised of the following:

	Year Ended December 31,	
	2017	2016
Deferred tax assets:		
U.S. and state net operating loss carryforwards	$ 84,556	$ 91,584
Stock-based compensation	15,748	17,004
Accruals and other temporary differences	2,386	2,491
Research and development credits	29,186	15,898
Capitalized research and development	2,211	3,344
Total deferred tax assets	134,087	130,321
Less valuation allowance	(134,087)	(130,321)
Net deferred tax assets	$ —	$ —

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on the Company's history of operating losses, the Company has concluded that it is more likely than not that the benefit of its deferred tax assets will not be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2017 and 2016. The valuation allowance increased by approximately $3,766 for tax year ended December 31, 2017 primarily due to the generation of net operating losses offset by the revaluation of the deferred assets at a 21% Federal tax rate.

The Company adopted ASU 2016-09, Improvements to Employee Share-Based Payment Accounting on January 1, 2017. As a result of adoption, the deferred tax assets associated with net operating losses as of December 31, 2016 have increased by $1,844. These amounts were offset by a corresponding increase in the valuation allowance. The adoption of ASU 2016-09 has no impact on the Company's operations, financial position or cash flows.

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,		
	2017	2016	2015
Federal income tax expense at statutory rate	34.0%	34.0%	34.0%
State income tax, net of federal benefit	5.9%	3.3%	3.5%
Permanent differences	(3.9)%	(3.1)%	(5.1)%
Research and development credit	8.4%	4.8%	12.2%
Foreign rate differential	(9.4)%	(8.5)%	(6.3)%
Change in valuation allowance	(1.4)%	(25.1)%	(39.4)%
Provision to return adjustments	1.0%	(5.5)%	—%
Other	(1.4)%	—%	1.0%
Federal rate change	(33.2)%	—%	—%
Effective income tax rate	—%	(0.1)%	(0.1)%

As of December 31, 2017 and 2016, the Company had U.S. federal net operating loss carryforwards of approximately $300,843 and $237,824, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2037. As of December 31, 2017 and 2016, the Company also had U.S. state net operating loss carryforwards of approximately $332,330 and $238,033, respectively, which may be available to offset future income tax liabilities and expire at various dates through 2037.

As of December 31, 2017 and 2016, the Company had federal research and development tax credit carryforwards of approximately $27,384 and $14,932, respectively, available to reduce future tax liabilities which expire at various dates through 2037. As of December 31, 2017 and 2016, the Company had state research and development tax credit carryforwards of approximately $2,282 and $1,463, respectively, available to reduce future tax liabilities which expire at various dates through 2032. The Company completed a study of its R&D tax credits through December 31, 2016 and adjusted its deferred tax asset for the result of that study. For the year ended December 31, 2017, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's 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 the Company's 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 the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception which resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, and it may complete future financings that could result in a change in control in the future. The Company has reduced its deferred tax assets for tax attributes it believes will expire unused due to the change in control limitations.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2017 and 2016, the Company had no accrued interest or penalties related to uncertain tax

positions and no such amounts have been recognized in the Company's statements of operations and comprehensive loss.

The Company or one of its subsidiaries files 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, 2014 through December 31, 2017. To the extent the Company has 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.

13. Subsequent Event

Biogen Asset Purchase Agreement

On January 24, 2018, the Company entered into an Asset Purchase Agreement (the "APA") with Biogen MA Inc., a Massachusetts corporation and subsidiary of Biogen, Inc. ("Biogen"), pursuant to which Biogen acquired exclusive worldwide rights to develop and commercialize the Company's oral Selective Inhibitor of Nuclear Export (SINE) compound KPT-350 and certain related assets with an initial focus in amyotrophic lateral sclerosis (ALS).

Under the terms of the APA, Biogen purchased KPT-350 and certain related assets and assumed certain related liabilities. The Company received a one-time upfront payment of $10,000 from Biogen and is eligible to receive additional payments of up to $207,000 based on the achievement by Biogen of future specified development and commercial milestones. The Company 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.

The Company 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 the Company regarding an assignment or license back to the Company 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 the Company under the APA.

14. Selected Quarterly Financial Information (Unaudited)

The following table summarizes the unaudited quarterly financial data for the last two fiscal years (in thousands).

Year Ended December 31, 2017	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
License and other revenue	$ 68	$ 3	$ —	$ 1,534
Total operating expenses	$ 30,347	$ 29,755	$ 31,055	$ 40,986
Loss from operations	$(30,279)	$(29,752)	$(31,055)	$(39,452)
Total other income (expense)	$ 385	$ 383	$ 428	$ 421
Net loss	$(29,917)	$(29,387)	$(30,640)	$(39,040)
Net loss per share, basic and diluted	$ (0.71)	$ (0.64)	$ (0.65)	$ (0.80)

Year Ended December 31, 2016	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Contract and grant revenue	$ —	$ 59	$ 48	$ 47
Total operating expenses	$ 27,349	$ 30,535	$ 25,790	$ 27,212
Loss from operations	$(27,349)	$(30,476)	$(25,742)	$(27,165)
Total other income (expense)	$ 290	$ 318	$ 317	$ 369
Net loss	$(27,059)	$(30,158)	$(25,425)	$(26,935)
Net loss per share, basic and diluted	$ (0.75)	$ (0.84)	$ (0.69)	$ (0.65)

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
3.1	Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on November 18, 2013)
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)
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*	2013 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.6 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 28, 2013)
10.8*	Form of Indemnification Agreement between the Registrant and each of its Directors (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 (File No. 333-191584) filed with the Commission on October 4, 2013)
10.9*	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)

Exhibit Number	Description of Exhibit
10.10*	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)
10.11*	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)
10.12*	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)
10.13*	Amended and Restated Letter Agreement, dated as of January 23, 2015, between the Registrant and Justin Renz (incorporated by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K filed with the Commission on January 23, 2015)
10.14*	Consulting Agreement, dated as of April 3, 2017, between the Registrant and Justin Renz (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed with the Commission on April 3, 2017)
10.15*	Separation Agreement, dated as of April 3, 2017, between the Registrant and Justin Renz (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed with the Commission on April 3, 2017)
10.16*	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)
10.17*	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)
10.18*	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)
10.19*	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)
10.20*	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)
10.21*	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)
10.22*	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)

Exhibit Number	Description of Exhibit
10.23	Office Lease Agreement between NS Wells Acquisition LLC and the Registrant, dated March 27, 2014 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on April 1, 2014)
10.24	First Amendment to Lease, dated December 31, 2014, by and between the Registrant and NS Wells Acquisition LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on January 5, 2015)
10.25	Second Amendment to Lease, dated October 22, 2015, by and between the Registrant and NS Wells Acquisition LLC (incorporated by reference to Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36167) filed with the Commission on November 9, 2015)
10.26†	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)
10.27	Controlled Equity Offering℠ Sales Agreement, dated December 7, 2015, by and between the Registrant and Cantor Fitzgerald & Co. (incorporated by reference to Exhibit 1.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on December 8, 2015)
10.28	Amendment No. 1 to Controlled Equity Offering℠ Sales Agreement, dated December 7, 2015, by and between the Registrant and Cantor Fitzgerald & Co., dated November 7, 2016 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on November 8, 2016)
10.29	Amendment No. 2 to Controlled Equity Offering℠ Sales Agreement, dated December 7, 2015, as amended on November 7, 2016, by and between the Registrant and Cantor Fitzgerald & Co., dated December 1, 2017 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36167) filed with the Commission on December 1, 2017)
10.30††	License Agreement, dated October 11, 2017, by and between the Registrant and Ono Pharmaceutical Co., Ltd.
12.1**	Statements Regarding Calculation of Consolidated Ratios of Earnings to Fixed Charges and Ratios of Earnings to Combined Fixed Charges and Preferred Stock Dividends
21.1**	Subsidiaries of the Registrant
23.1**	Consent of Ernst & Young LLP (Independent registered public accounting firm for the Company)
31.1**	Certification of Chief Executive Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2**	Certification of Executive Vice President, Chief Financial Officer and Treasurer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1**	Certifications pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of The Sarbanes-Oxley Act of 2002, by Michael G. Kauffman, M.D., Ph.D., Chief Executive Officer of the Registrant, and Michael F. Falvey, Executive Vice President, Chief Financial Officer and Treasurer of the Registrant

Exhibit Number	Description of Exhibit
101.INS XBRL	Instance Document
101.SCH XBRL	Schema Document
101.CAL XBRL	Calculation Linkbase Document
101.LAB XBRL	Labels Linkbase Document
101.PRE XBRL	Presentation Linkbase Document
101.DEF XBRL	Definition Linkbase Document

† Confidential treatment has been granted as to portions of the exhibit.
†† Confidential treatment has been requested for certain portions which are omitted in the copy of the exhibit electronically filed with the Commission. The omitted information has been filed separately with the Commission pursuant to the Company's application for confidential treatment.
* Indicates a management contract or compensatory plan or arrangement.
** Filed with this Annual Report on Form 10-K.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

KARYOPHARM THERAPEUTICS INC.

Date: March 15, 2018

By: /s/ Michael G. Kauffman
Michael G. Kauffman, M.D., Ph.D.
Chief Executive Officer and Director
(Principal Executive Officer)

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Michael G. Kauffman Michael G. Kauffman, M.D., Ph.D.	Chief Executive Officer and Director *(Principal Executive Officer)*	March 15, 2018
/s/ Michael F. Falvey Michael F. Falvey	Executive Vice President, Chief Financial Officer and Treasurer *(Principal Financial and Accounting Officer)*	March 15, 2018
/s/ Garen G. Bohlin Garen G. Bohlin	Director	March 15, 2018
/s/ Mikael Dolsten Mikael Dolsten, M.D., Ph.D.	Director	March 15, 2018
/s/ J. Scott Garland J. Scott Garland	Director	March 15, 2018
/s/ Barry E. Greene Barry E. Greene	Director	March 15, 2018
/s/ Deepika R. Pakianathan Deepika R. Pakianathan, Ph.D.	Director	March 15, 2018
/s/ Mansoor Raza Mirza Mansoor Raza Mirza, M.D.	Director	March 15, 2018
/s/ Kenneth E. Weg Kenneth E. Weg	Director	March 15, 2018

Exhibit 10.30

Confidential Materials omitted and filed separately with the
Securities and Exchange Commission. Double asterisks denote omissions.

LICENSE AGREEMENT

by and between

KARYOPHARM THERAPEUTICS INC.

and

ONO PHARMACEUTICAL CO., LTD.

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SCHEDULES

LICENSE AGREEMENT

THIS LICENSE AGREEMENT (this "**Agreement**"), effective as of October 11, 2017 (the "**Effective Date**"), is made and entered into by and between Karyopharm Therapeutics Inc., a corporation organized and existing under the laws of the State of Delaware, having an address at 85 Wells Avenue, Suite 210, Newton, MA 02459 USA ("**Karyopharm**"), and Ono Pharmaceutical Co., Ltd., a corporation organized and existing under the laws of Japan, having an address at 8-2, Kyutaro-machi 1-chome, Chuo-ku, Osaka, Osaka 541-8564, Japan ("**Ono**"). Karyopharm and Ono are sometimes referred to herein individually as a "**Party**" and collectively as the "**Parties**."

RECITALS:

WHEREAS, Karyopharm owns or Controls certain intellectual property relating to the Licensed Compounds and the Licensed Products (each as defined below);

WHEREAS, Ono desires to Develop and Commercialize Licensed Compounds and Licensed Products in the Field in the Ono Territory (each as defined below);

WHEREAS, Karyopharm and Ono believe that a license for such purpose on the terms and conditions of this Agreement would be desirable.

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants herein contained, the Parties hereby agree as follows:

1. DEFINITIONS

Unless specifically set forth to the contrary herein, the following terms, whether used in the singular or plural, shall have the respective meanings set forth below:

1.1 "Affiliate" means, as to a specified Person, another Person that, directly or indirectly, controls, is controlled by, or is under common control with the Person specified, for so long as such control continues. An entity will be regarded as in control of another entity if: (a) it owns, directly or indirectly, more than fifty percent (50%) of the voting securities or capital stock of such entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (b) it possesses, directly or indirectly, the power to direct or cause the direction of the management and policies of the corporation or non-corporate business entity, as applicable, whether through the ownership or control of voting securities, by contract or otherwise.

1.2 "**Annual Net Sales**" means the Net Sales generated over any given Ono Fiscal Year.

1.3 "**Back-Up Compound**" means, with respect to a Lead Compound, any compound that (a) is Developed by Karyopharm for use in the Field, (b) inhibits the nuclear export protein Exportin 1, or XPO1, and (c) is designated by JOC as a back-up compound to such Lead Compound in accordance with Section 2.7.2.

1.4 "**Business Day**" means any day other than a day which is a Saturday, a Sunday, any day banks are authorized or required to be closed in the United States or Japan or any day within Karyopharm's corporate holidays (for Karyopharm's obligations) or Ono's corporate holidays (for Ono's obligations).

1.5 "**Calendar Quarter**" means the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30, and December 31 of each Calendar Year; provided that the first Calendar Quarter of the Term shall begin on the Effective Date and end on the first to occur of March 31, June 30, September 30 or December 31 thereafter and the last Calendar Quarter of the Term shall end on the last day of the Term.

1.6 "**Calendar Year**" means each successive period of twelve (12) calendar months commencing on January 1 and ending on December 31; provided that the first Calendar Year of the Term shall begin on the Effective Date and end on the first December 31 thereafter and the last Calendar Year of the Term shall end on the last day of the Term.

1.7 "**CDE**" means the Center of Drug Evaluation, Taiwan and any successor Governmental Authority having substantially the same function.

1.8 **"CDISC"** means Clinical Data Interchange Standards Consortium which is an interdisciplinary nonprofit organization that establishes international standards for data collection, interchange, application, and storage for the purpose of promoting interoperation of clinical research data.

1.9 "**Clinical Data**" means all information relating to Licensed Compounds and/or Licensed Products made, collected or otherwise generated in the performance of or in connection with any Clinical Study, including any data, reports and results relating thereto (including clinical data and other related information generated in compliance with CDISC standards).

1.10 "**Clinical Study**" means a clinical trial in humans, including a Phase I Study, Phase II Study, Phase III Study, an Ono Post-Registration Study, a Karyopharm post-registration study or a Global Clinical Study.

1.11 "**Combination Product**" means any pharmaceutical product containing both a Licensed Product component and one or more other active pharmaceutical ingredients.

1.12 "**Commence**" or "**Commencement**" means, with respect to a Clinical Study of a Licensed Product, the first dosing of the first human subject with such Licensed Product in such Clinical Study.

1.13 "**Commercialization**" or "**Commercialize**" means any and all activities directed to marketing, promoting, distributing, importing, exporting, offering to sell and/or selling a Licensed Product and activities directed to obtaining pricing and reimbursement approvals, as applicable.

1.14 "**Commercially Reasonable Efforts**" means the carrying out of obligations in a diligent and sustained manner using such effort and employing such resources as would normally be exerted or employed by a Party or its Affiliates for a product that is of similar market potential

at a similar stage in its Development or product life, taking into account all relevant factors, including the potential profitability of the product, the costs and risks of Developing, Manufacturing, having Manufactured, use and Commercializing the product, scientific, safety and regulatory concerns, product profile, the competitiveness of the marketplace and the proprietary position of the product.

Without limiting the foregoing,

(a) in relation to Development activities, including for purposes of obtaining Regulatory Approval of a product, "**Commercially Reasonable Efforts**" require that such Party: (i) assign responsibility for the relevant activities to specific employees who are responsible for progress and monitor such progress on a regular basis; (ii) set and consistently seek to achieve specific and meaningful objectives and timelines for carrying out such activities; and (iii) consistently make and implement decisions and allocate resources consistent with the efforts described above; and

(b) in relation to requiring Related Party to conduct certain activities under this Agreement, "**Commercially Reasonable Efforts**" require that (i) to the extent that such Related Party is its Affiliate, each Party oblige such Related Party to accept terms and conditions equivalent to those set forth in this Agreement, (ii) to the extent that such Related Party is a Third Party Licensee or a Sublicensee, each Party negotiate with such Related Party and use good faith efforts to persuade it to accept terms and conditions, which, to the maximum extent, will be consistent with those set forth in this Agreement and (iii) each Party exercise all of its rights and performs the obligations under any agreement between such Party and such Related Party in a commercially appropriate and timely manner so that the purpose of this Agreement contemplated in each Section will be achieved.

1.15 "**Confidential Information**" means any and all information and data, including all scientific, non-clinical, pre-clinical, clinical, regulatory, Manufacturing, marketing, financial, trade secret and commercial information or Data, whether communicated in writing or orally or by any other method, which is provided by or on behalf of one Party or any of its Related Parties (the "**Disclosing Party**") to the other Party or any of its Related Parties (the "**Receiving Party**") in connection with this Agreement. Notwithstanding anything to the contrary set forth herein, (a) Karyopharm Technology (other than Joint IP) is the Confidential Information of Karyopharm; (b) Ono Technology (other than Joint IP) is the Confidential Information of Ono; and (c) Joint IP which has not yet been publicly disclosed shall be deemed to be the Confidential Information of both Parties; and (d) the terms of this Agreement shall be deemed to be the Confidential Information of both Parties. All information and data disclosed prior to the Effective Date by or on behalf of either Party under, and subject to, the Confidentiality Agreement, dated as of April 24, 2017, between the Parties (the "**Prior CDA**") shall be deemed the Confidential Information hereunder and such Party shall be deemed the Disclosing Party of such information and data hereunder and the other Party shall be deemed the Receiving Party hereunder. "**Confidential Information**" shall not include information or data, to the extent that such information or data:

1.15.1 is lawfully in the Receiving Party's possession prior to disclosure by the Disclosing Party and was not acquired directly or indirectly from Disclosing Party, as documented by the Receiving Party's business records;

1.15.2 is generally known to the public prior to its receipt by the Receiving Party, or thereafter becomes generally known to the public through no fault of the Receiving Party or any of its Related Parties with whom the Receiving Party shared the Confidential Information;

1.15.3 is subsequently disclosed to the Receiving Party by a Third Party that lawfully has possession of and the right to disclose such Confidential Information without the breach of any contractual, legal or fiduciary obligation to the Disclosing Party or any Third Party and provided that such Third Party is not disclosing on behalf of the Disclosing Party; or

1.15.4 is independently developed by the Receiving Party without use of or reference to Disclosing Party's Confidential Information, as documented by the Receiving Party's business records.

1.16 "**Control**" means, subject to the provisions of Section 14.1, with respect to a Party and/or its Related Party, as the case may be, and any Know-How, Patent Right or other intellectual property right, the possession (whether by ownership or license, other than a license granted to such Party pursuant to this Agreement) of the ability of such Party or any such Related Party to transfer, grant access to, or grant a license or sublicense of, such Know-How, Patent Right or other intellectual property right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party.

1.17 **"Cost of Manufacturing"** means, to the extent that Manufacturing of a Licensed Compound, Licensed Product or any component thereof is performed by a Party itself or by its Affiliate, the actual consolidated, fully burdened cost incurred by such a Party and its Affiliates to Manufacture such a Licensed Compound, Licensed Product or any component thereof, including: (a) direct labor costs (salaries, wages, incentive compensation, share-based compensation and employee benefits); (b) direct materials and packaging costs; (c) operating costs of facilities and equipment, excluding any surplus or idle capacity costs; (d) a charge for depreciation, repairs and maintenance costs of facilities and equipment; (e) quality and in-process control costs; (f) a charge for overhead costs for raw material and manufacturing administration and management, materials management, storage and handling, and manufacturing and employee training; (g) charges for spoilage, scrap, rework costs and expired goods; and (h) inbound and outbound freight, shipping insurance, excise taxes and customs duties; in each of the above cases to the extent reasonably allocable to Manufacture of such Licensed Compound, Licensed Product or component as determined in accordance with GAAP or IFRS, as applicable, consistently applied.

1.18 "**Cover**," "**Covering**" or "**Covers**" means that in the absence of ownership of or a license granted under a Valid Claim, the Development, Manufacture, having Manufactured, use or Commercialization of a Licensed Compound or a Licensed Product would infringe such Valid Claim (or, in the case of a Valid Claim that has not yet issued, would infringe such Valid Claim if it were to issue).

1.19 "**Data**" means any and all scientific, technical, test and patient exposure data pertaining to any Licensed Compound or Licensed Product that are necessary or useful for the Development, Manufacture, having Manufactured, use and/or Commercialization of each

Licensed Compound and Licensed Product in the Field and that are Controlled by Ono and/or its Related Parties or Controlled by Karyopharm and/or its Related Parties, including research data, clinical pharmacology data, non-clinical data, pre-clinical data and Clinical Data.

1.20 "**Development**" or "**Develop**" means non-clinical, pre-clinical and clinical research and development activities, including the design or identification of a compound, drug metabolism and pharmacokinetics, translational research, toxicology, pharmacology toxicology studies, statistical analysis and report writing, pre-clinical testing, formulation development, Clinical Studies, regulatory affairs (including preparation for NDA submission and other submission-related activities), product approval and registration activities, and all other activities necessary to seek, obtain and maintain Regulatory Approval; provided, however, that Development shall not include Commercialization and Manufacturing.

1.21 "**Executive Officer**" means the Chief Executive Officer or his or her designee in the case of Karyopharm, and Executive Director or his or her designee in the case of Ono.

1.22 "**Field**" means the diagnosis, treatment and/or prevention of cancer in humans.

1.23 "**First Commercial Sale**" means, with respect to a country in the Ono Territory, the first sale for end use or consumption of the Licensed Product in such country after all Regulatory Approvals legally required for such sale have been granted by the Regulatory Authority of such country or, if Regulatory Approval is not required, after the date on which sales are permitted by applicable Law.

1.24 "**GAAP**" means generally accepted accounting principles of the United States.

1.25 "**GCP**" means the current standards for clinical studies for pharmaceuticals, as set forth in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines and applicable regulations promulgated thereunder, as amended from time to time.

1.26 "**Global Clinical Study**" means a combined Phase I Study and Phase II Study, a combined Phase II Study and Phase III Study, a Phase II Study or a Phase III Study, of a Licensed Product in the Field which includes sufficient [**] clinical sites and/or [**] patients to achieve Regulatory Approval in both the Ono Territory and the Karyopharm Territory for the Indication associated with such Clinical Study.

1.27 **"Global Common Costs"** means the direct development costs that are incurred by a Party in connection with the Global Common Activity.

1.28 "**GLP**" means the current standards for laboratory activities for pharmaceuticals, as set forth in the FDA's Good Laboratory Practice regulations or the Good Laboratory Practice principles of the Organization for Economic Co-Operation and Development, as amended from time to time, and such standards of good laboratory practice as are required by the MHLW and other organizations and Governmental Authorities in countries in which a Licensed Product is intended to be sold, to the extent such standards are not less stringent than United States Good Laboratory Practice.

1.29 "**GMP**" means all Laws and guidelines applicable to Manufacture of the Licensed Compound or Licensed Product, including (a) the FD&C Act (21 U.S.C. 321 et seq.); (b) relevant United States regulations in Title 21 of the United States Code of Federal Regulations (including Parts 11, 210, and 211); (c) European Community Directives 2001/83/EC and 2003/94/EC; (d) the EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, as set out in Volume 4 of the European Commission's Rules governing medicinal products in the EU; (e) those standards required by the MHLW; (f) ICH, Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients; (g) similar standards and Laws to those in (a) through (f), as are in effect at the time of Manufacture of the Licensed Compound and/or Licensed Product; and (h) all additional Regulatory Authority documents or regulations that replace, amend, modify, supplant or complement any of the foregoing.

1.30 "**Governmental Authority**" means any multinational, federal, national, state, provincial, local or other entity, office, commission, bureau, agency, political subdivision, instrumentality, branch, department, authority, board, court, arbitral or other tribunal, official or officer, exercising executive, judicial, legislative, police, regulatory, administrative or taxing authority or functions of any nature pertaining to government.

1.31 **"IFRS"** means International Financial Reporting Standards.

1.32 "**IND**" means an Investigational New Drug application, Clinical Trial Application or similar application or submission for approval to conduct human clinical investigations filed with or submitted to a Regulatory Authority in conformance with the requirements of such Regulatory Authority.

1.33 "**Indication**" means an indication by tumor type but not by line therapy of each tumor or cancer. By way of explanation, (a) an "**Indication**" shall be considered the same if the subject cancer has the same organ of origin even if they are, for example, of a different histologic or genetic subtype, a different cell type or a different line of therapy, and (b) "**Indication**" shall be considered different if the subject cancers have different organs of origin.

1.34 "**Investigator Sponsored Clinical Study**" means a clinical study or research of a Licensed Product in the Field that is sponsored and conducted by a physician, physician group or other Third Party not acting on behalf of a Party or its Related Party and who does not have a license from a Party or its Related Party to Commercialize such Licensed Product, pursuant to an IND owned by such Third Party in the case of a clinical study, and with respect to which a Party or its Related Party provides clinical supplies of the Licensed Product, funding or other support for such clinical study or research.

1.35 "**Joint IP**" means, collectively, Joint Patent Rights and Joint Know-How.

1.36 "**Joint Know-How**" means (a) any Know-How generated in course of the Global Clinical Study which is related to the combination of a Licensed Product and a commercial product or product in clinical development in either case owned by or licensed to Ono and (b) any Know-How that is (i) not solely related to Licensed Product or a commercial product or product in clinical development in either case owned by or licensed to Ono and (ii) first made or identified, discovered or developed jointly by director(s), officer(s), employee(s), agent(s) or consultant(s)

acting on behalf of Karyopharm or its Affiliates, on the one hand, and director(s), officer(s), employee(s), agent(s) or consultant(s) acting on behalf of Ono or its Affiliates, on the other hand. All other Know-How generated in relation to the Global Clinical Study shall not be Joint Know-How and shall be Karyopharm Know-How and subject to the license grant to Ono described in Section 7.1.1.

1.37 "**Joint Operating Committee**" or "**JOC**" means the joint operating committee as more fully described in Section 5.1.

1.38 **"Joint Patent Rights"** means any Patent Rights that (a) Cover Joint Know-How and (b) are Controlled by Karyopharm and Ono.

1.39 "**Karyopharm Know-How**" means all Know-How, which, as of the Effective Date and during the Term, is Controlled by Karyopharm and/or any of its Affiliates, which (a) are not generally known, (b) are not Covered by a Karyopharm Patent Rights, (c) relates to any Licensed Compound and/or Licensed Product and (d) are necessary or useful for the research, Development, Manufacture, having Manufactured, use and/or Commercialization of each Licensed Compound and Licensed Product in the Field; provided, however, that Karyopharm Know-How excludes the Joint Know-How.

1.40 "**Karyopharm Patent Rights**" means all Patent Rights which, as of the Effective Date of and during the Term, are Controlled by Karyopharm and/or any of its Affiliates, and which claim or Cover, are necessary or useful for or would be practiced by the research, Development, Manufacture, having Manufactured, use, and/or Commercialization of each Licensed Compound and Licensed Product in the Field; provided, however, that Karyopharm Patent Rights excludes Joint Patent Rights.

1.41 "**Karyopharm Technology**" means, collectively, Karyopharm Know-How, Karyopharm Patent Rights and Karyopharm's interest in Joint IP.

1.42 "**Karyopharm Territory**" means all countries and territories of the world other than the Ono Territory.

1.43 "**Karyopharm Third Party Agreements**" means (a) those agreements listed on Schedule 1.43 and (b) any agreements entered into as of the Effective Date by Karyopharm or any of its Affiliates pursuant to which Karyopharm Controls any Karyopharm Technology or receives funding to develop any Karyopharm Technology or any Licensed Compound or Licensed Product (unless solely for use outside the Field).

1.44 "**Knowledge**" means actual knowledge of department head and working team member(s) on function-by-function basis for or on behalf of each Party. For clarity, such actual knowledge shall be obtained and finalized after making due and appropriate inquiry with respect to the particular matter in question.

1.45 "**Know-How**" means all technical information, know-how and data, including trade secrets, inventions (whether patentable or not), discoveries, methods, specifications, processes, expertise, technology, Data, other non-clinical, pre-clinical and Clinical Data and results

(including pharmacological, toxicological, biological, chemical, physical, safety and manufacturing data and results), analytical and quality control data and results, regulatory filings and documents, and other information. "**Know-How**" excludes in any event any Patent Rights.

1.46 "**KPT-8602**" means the compound known as KPT-8602, which is described on Schedule 1.46.

1.47 "**Law**" means any law, statute, rule, regulation, court order, ordinance or other pronouncement having the effect of law, of any Governmental Authority, including (a) good clinical practices and adverse event reporting requirements, guidance from the ICH or other generally accepted conventions, and all rules, regulations, requirements and guidances of applicable Regulatory Authorities, (b) all export control and sanctions laws, and (c) the rules of any stock exchange or listing entity.

1.48 "**Lead Compound**" means Selinexor or KPT-8602, as applicable.

1.49 "**Licensed Compound**" means a Lead Compound, which Lead Compound may be replaced by a Back-Up Compound in accordance with Section 2.7.2.

1.50 "**Licensed Product**" means any pharmaceutical product comprising or containing a Licensed Compound as an active ingredient, in any dosage form or formulation. As used in this Agreement, except where not appropriate in context, "**Licensed Product**" also means the Licensed Compound contained in the relevant Licensed Product. In calculation of the Royalty Term pursuant to Section 8.4.1, to the extent that a Licensed Compound is contained as a sole active ingredient, any formulation, including but not limited to a tablet, a capsule, a powder, a granule, a liquid, an intravenous, a subcutaneous injection or a patch formulation, any such formulated Licensed Product shall be deemed as same Licensed Product. Further, it is understood by the Parties that a Combination Product containing a Licensed Compound as one of active ingredients shall be deemed as a Licensed Product, which is different from a Licensed Product containing a Licensed Compound as a sole active ingredient.

1.51 "**Losses**" means any losses, liabilities, damages, costs, fees and expenses (including reasonable attorneys' fees and litigation expenses) arising out of or relating to suits or claims brought by Third Party (including product liability claims).

1.52 "**Manufacturing**" or "**Manufacture**" means, as applicable, all activities associated with the production, manufacture, processing, filling, finishing, quality assurance testing and release, stability studies, process validation, analytical development, packaging, labeling, shipping and storage of a pharmaceutical product, (including production of drug substance and drug product, in bulk form, for preclinical studies, Clinical Studies or Commercialization); provided, however, that Manufacturing shall not include Development and Commercialization. When used as a verb, "to Manufacture" and "Manufacturing" mean to engage in Manufacture, and "Manufactured" has a corresponding meaning.

1.53 "**Mechanism of Action**" means the binding to the nuclear export protein, Exportin 1, or XPO1, causing inhibition of the activity of XPO1 or otherwise reducing the nuclear export of XPO1's cargo proteins.

1.54 "**MFDS**" means the Ministry of Food and Drug Safety in the Republic of Korea and any successor Governmental Authority having substantially the same function.

1.55 "**MHLW**" means the Japanese Ministry of Health, Labour and Welfare and any successor Governmental Authority having substantially the same function.

1.56 "**NDA**" means a New Drug Application, Biologics License Application, Marketing Authorization Application or similar application or submission filed with a Regulatory Authority in a country or group of countries to obtain marketing approval for a pharmaceutical product in such country or such group of countries.

1.57 "**Net Sales**" means the gross amount invoiced on sales of Licensed Products in the Field within the Ono Territory by Ono or any of its Related Parties to any Third Party, less the following sum incurred by Ono or any of its Related Parties, with respect to the sale of such Licensed Products, calculated in accordance with IFRS as consistently applied:

1.57.1 normal trade, cash, quantity and other customary discounts actually given to Third Parties in the ordinary course of business;

1.57.2 rebates, credits and allowances given by reason of rejections returns, damaged or defective product or recalls;

1.57.3 government-mandated rebates and any other compulsory payments, credits, adjustments and rebates actually paid or deducted;

1.57.4 any sales-based contributions actually made for "Contributions for Drug Induced Suffering", "Contribution for Measure for Drug Safety" or any other contributions for aiding drug suffering in the amount determined by and payable to PMDA or any other Governmental Authority or industry organization in the Ono Territory;

1.57.5 price adjustments, allowances, credits, chargeback payments, discounts, rebates, fees and reimbursements or similar payments granted or made to managed care organizations, group purchasing organizations or other buying groups, pharmacy benefit management companies, health maintenance organizations and any other providers of health insurance coverage, health care organizations or other health care institutions (including hospitals), health care administrators, patient assistance or other similar programs, or to federal state/provincial, local and other governments, including their agencies, or to wholesalers, distributors or other trade customers;

1.57.6 a fixed amount of [**] percent ([**]%) of gross sales to cover reasonable and customary freight, shipping, insurance and other transportation expenses;

1.57.7 sales, consumption or excise taxes, tariffs and duties, and other taxes and government charges directly related to the sale, delivery or use of Licensed Product (but not including taxes assessed directly against the income derived from such sale); and

1.57.8 a reasonable deduction to reflect amounts previously included in Net Sales of Licensed Product that are written off as uncollectible after reasonable collection efforts, in accordance with standard practices of Ono.

Notwithstanding anything in this Agreement to the contrary, the transfer of a Licensed Product between or among Ono and any of its Affiliates and Sublicensees will not be considered a sale.

Disposition of a Licensed Product for, or use of a Licensed Product in, Clinical Studies or other scientific testing, as free samples, or under compassionate use, patient assistance, or test marketing programs or other similar programs or studies shall not result in Net Sales.

Net Sales will be determined from books and records maintained in accordance with IFRS, consistently applied throughout Ono.

In the event a Licensed Product is sold in the form of a Combination Product, then the Net Sales for any such Combination Product shall be determined by multiplying the Net Sales of the Combination Product during the applicable royalty reporting period, by the fraction, A/(A+B+…+N), where A is the weighted (by sales volume) average sale price of the Licensed Product component when sold separately in finished form in the country in which the Combination Product is sold, and B+ … +N are the weighted (by sales volume) average sale prices of the other active pharmaceutical ingredients included in the Combination Product when sold separately in finished form in the country in which the Combination Product is sold, in each case during the applicable royalty reporting period or, if sales of both the Licensed Product component and the other active pharmaceutical ingredients did not occur in such period, then in the most recent royalty reporting period during the preceding twelve (12) months in which sales of both occurred, if any. In the event that such average sale price cannot be determined for the Licensed Product and/or all other active pharmaceutical ingredients included in the Combination Product, then the Parties will in good faith discuss and agree on a pro-rata allocation of the Net Sales that reflects the Licensed Product's contribution to the Combination Product on an equitable basis.

1.58 "**Ono Fiscal Year**" means each successive period of twelve (12) calendar months commencing on April 1 of a particular Calendar Year and ending on March 31 of the immediately following Calendar Year.

1.59 "**Ono Know-How**" means (a) all Know-How, which, as of the Effective Date and during the Term, is Controlled by Ono and its Affiliates, which (i) are not generally known, (ii) are not Covered by a Ono Patent Rights, (iii) relates to any Licensed Compound and/or Licensed Product and (iv) are necessary or useful for the research, Development, Manufacture, having Manufactured, use and/or Commercialization of each Licensed Compound and Licensed Product in the Field and (b) any Know-How generated in course of the Global Clinical Study which is only related to a commercial product or product in clinical development in either case owned by or licensed to Ono; provided, however, that Ono Know-How excludes Joint Know-How.

1.60 "**Ono Patent Rights**" means all Patent Rights Controlled by Ono and its Affiliates, as of the Effective Date and during the Term, which claim or Cover, are necessary or useful for or would be practiced by the research, Development, Manufacture, having Manufactured, use and/or Commercialization of Licensed Products in the Field; provided, however, that Ono Patent Rights excludes Joint Patent Rights.

1.61 "**Ono Post-Registration Studies**" means any clinical studies of a Licensed Product conducted by Ono or any of its Related Parties following receipt of Regulatory Approval for a Licensed Product necessary to maintain its Regulatory Approval.

1.62 "**Ono Technology**" means, collectively, Ono Know-How, Ono Patent Rights and Ono's interest in Joint IP.

1.63 "**Ono Territory**" means the following countries, as may be amended in accordance with this Agreement: Japan, Republic of Korea, Republic of China (known as Taiwan), Hong Kong, Brunei, Cambodia, Indonesia, Laos, Malaysia, Mayanmar, Philippines, Singapore, Thailand, and Vietnam.

1.64 "**Patent Rights**" means (a) all issued patents (including extensions, restorations by existing or future extension or registration mechanisms, including patent term adjustments, patent term extensions, supplemental protection certificates or the equivalent thereof, substitutions, confirmations, re-registrations, re-examinations, and patents of addition), (b) patent applications (including all provisional applications, substitutions, requests for continuation, continuations, continuations-in-part, divisionals and renewals), (c) inventor's certificates, and (d) all equivalents of the foregoing in any country of the world.

1.65 "**Person**" means any natural person, corporation, unincorporated organization, partnership, association, sole proprietorship joint stock company, joint venture, limited liability company, trust or government, or any agency or political subdivision of any government, or any other similar entity.

1.66 "**Phase I Study**" means a study in humans which provides for the introduction into humans of a pharmaceutical product, conducted in healthy volunteers or patients, to obtain initial information on product safety, tolerability, pharmacological activity or pharmacokinetics, as more fully defined in 21 C.F.R. § 312.21(a) (or the equivalent thereof outside the United States).

1.67 "**Phase II Study**" means a study in humans of the safety, dose ranging or efficacy of a pharmaceutical product, as further defined in 21 C.F.R. § 312.21(b) (or the equivalent thereof outside the United States).

1.68 "**Phase III Study**" means a study in humans of the efficacy and safety of a pharmaceutical product, which is prospectively designed to demonstrate whether such product is effective and safe for use in a particular indication in a manner sufficient (alone or together with one or more other such studies) to file an application for Regulatory Approval for the product.

1.69 "**PMDA**" means the Pharmaceuticals and Medical Devices Agency in Japan and any successor Governmental Authority having substantially the same function.

1.70 "**Regulatory Approval**" means any and all approvals, licenses, registrations or authorizations of any Regulatory Authority that are necessary for the marketing and sale of a pharmaceutical product in a country or group of countries, including NDAs and orphan drug designations.

1.71 "**Regulatory Authority**" means any applicable government regulatory authority involved in granting approvals for the Development, Manufacturing or Commercialization of a pharmaceutical product, including, as applicable, the MHLW, PMDA, CDE and MFDS.

1.72 "**Regulatory Exclusivity**" means any exclusive marketing rights or data exclusivity rights conferred by any Regulatory Authority with respect to any Licensed Product that precludes the use of any Clinical Data collected and filed for such Licensed Product for the benefit of any Regulatory Approval for a generic or biosimilar product (for any use), including any orphan or pediatric exclusivity where applicable.

1.73 "**Related Party**" means (a) with respect to Karyopharm, Karyopharm's Affiliates or any of its Third Party Licensee, and (b) with respect to Ono, Ono's Affiliates and permitted Sublicensees.

1.74 "**Selinexor**" means the compound known as KPT-330, which is described on Schedule 1.74.

1.75 "**Sublicensee**" means a Third Party to whom Ono grants a sublicense under any Karyopharm Technology to (a) Develop, use or Commercialize a Licensed Compound or Licensed Product in the Field in the Ono Territory or (b) Manufacture or have Manufactured Licensed Compound or Licensed Product in the Field for the Ono Territory, pursuant to Section 7.2.1.

1.76 "**Territory**" means (a) with respect to Karyopharm, the Karyopharm Territory, and (b) with respect to Ono, the Ono Territory.

1.77 "**Third Party**" means a Person other than a Party and its Affiliates.

1.78 "**Third Party Licensee**" means Karyopharm's licensees of the Karyopharm Technology in the Karyopharm Territory.

1.79 "**United States**" or "**U.S.**" means the United States of America and its territories, possessions and commonwealths.

1.80 "**Valid Claim**" means any claim in any (a) unexpired and issued patent that has not been disclaimed, revoked or held invalid by a final nonappealable decision of a court or other governmental agency of competent jurisdiction, or (b) to the extent that Karyopharm prosecutes in timely manner pursuant to Section 12.4.2(a), patent application that has not lapsed, in the case of a provisional patent application, or been cancelled, withdrawn or abandoned without the possibility of revival, nor has been pending for more than ten (10) years from the earliest priority date claimed for such application; provided, however, that, if, thereafter, a patent containing such claim matures into registered patent, such claim shall thereafter be considered a Valid Claim in accordance with subclause (a) above.

1.81 Additional Definitions. Each of the following definitions is set forth in the Section of this Agreement indicated below:

Definition:	Section:
1974 Convention	14.2
Agreement	Preamble
Auditing Party	8.6.1
Auditor	8.6.1
Change in Control	14.1
Clinical Quality Agreement	6.1.2
Clinical Supply Agreement	6.1.2
Collaboration Provisions	7.1.3
Commercial Supply Agreement	6.2.2
Common Brand Name	12.9.1
Competitive Infringement	12.5.1
CRO(s)	2.1
Development Milestone Event	8.2.1
Development Milestone Payment(s)	8.2.1
Disclosing Party	1.15
Disputes	14.3.1
Effective Date	Preamble
Generic Version	8.4.2
Global Clinical Development Plan	2.5.1
Global Clinical Study Proposal	2.5.2(a)
Global Common Activity	2.6.2
Global Development Working Group	5.5
Indemnitee	11.3
Infringement Action	12.6.1
Initiating Party	12.5.3
IP Working Group	5.5
JOC Chairpersons	5.1.3
Joint Patent Costs	12.4.3 (c)
Joint IP Prosecuting Party	12.4.3 (a)
Karyopharm	Preamble
Karyopharm Development Plan	2.4
Karyopharm Indemnitees	11.1
[**]	[**]
Liaison	5.6
Manufacturing Technology Transfer Plan	6.2.3
Ono	Preamble
Ono Development Plan	2.3
Ono Indemnitees	11.2
Overview Plan	2.2
Party/Parties	Preamble
Patent Challenge	13.4
Pre-Existing Affiliates	14.1

Definition:	Section:
Prior CDA	1.15
Receiving Party	1.15
Relevant Clinical Studies	2.1
Royalty Report	8.5
Royalty Term	8.4.1
Sales Milestone Event	8.3.1
Sales Milestone Payment(s)	8.3.1
SDEA	3.3
SPC	12.8.1
Subject Party	12.6.1
Sublicense	7.2.3
Term	13.1
Third-Country Currency	8.8.3
Working Group	5.5

2. DEVELOPMENT

2.1 Overview. The Parties acknowledge and agree that the Development of the Licensed Products for each Licensed Compound on a global basis is desirable for maximizing such Licensed Products' value, and therefore that exchange of each Party's and/or its Related Party's Development strategy in a transparent manner is imperative for such maximization. Prior to the Effective Date, Karyopharm has been engaged in the Development of the Licensed Compounds and the Licensed Products, including, with respect to each of the Licensed Products, sponsoring the conduct of the Clinical Studies set forth on Schedule 2.1 attached hereto (the "**Relevant Clinical Studies**"). Karyopharm shall use Commercially Reasonable Efforts to complete, at its own cost and expense, the Relevant Clinical Studies (including all pharmacovigilance aspects), including contracting and managing any contract research organization(s) ("**CRO(s)**") that may be involved in such Relevant Clinical Studies, and Karyopharm shall keep the JOC informed of the status thereof conducted by Karyopharm or its Related Party. Subject to the terms of this Agreement and in accordance with this Article 2, with respect to each Licensed Product, Ono shall assume responsibility for the Development of Licensed Products in the Field in the Ono Territory and Karyopharm shall assume responsibility for the Development of Licensed Products in the Field in the Karyopharm Territory.

2.2 Overview Plan. The Parties have agreed to an overview of the key steps and timelines for Development of the Licensed Compounds and the Licensed Products in the Field in both the Ono Territory and the Karyopharm Territory as outlined in Schedule 2.2 attached hereto (the "**Overview Plan**").

2.3 Development Plans for the Ono Territory. Within [**] after the Effective Date, Ono shall prepare and submit to the JOC for review and discussion a written plan for the Development of the Licensed Product in the Ono Territory (each, a "**Ono Development Plan**")

containing Selinexor setting forth the objectives of the Development to be conducted by Ono, a plan for the conduct of Clinical Studies by or on behalf of Ono or any of its Related Parties in the Ono Territory relating to the applicable Licensed Products containing Selinexor, the Development activities to be undertaken with respect to such Licensed Products containing Selinexor by or on behalf of Ono in the Field in the Ono Territory and a time table for the conduct of such activities, which Ono Development Plan shall be consistent with the Overview Plan and include a planning horizon of [**]. By the [**] of the Effective Date, Ono shall prepare and submit to the JOC for review and discussion an Ono Development Plan for the Licensed Product containing KPT-8602 setting forth the objectives of the Development to be conducted by Ono, the Development activities to be undertaken with respect to such Licensed Products containing KPT-8602 by or on behalf of Ono in the Field in the Ono Territory and a time table for the conduct of such activities. Ono will present any proposed amendments to each Ono Development Plan to the JOC for the JOC's review and discussion reasonably in advance of Ono's intention to implement such plans or amendments, including any amendments required under Section 2.7.2 below. For each Ono Development Plan, Ono shall also prepare and submit an updated Ono Development Plan to the JOC for the JOC's review and discussion [**].

2.4 Development Plans for the Karyopharm Territory. Karyopharm shall and/or shall use Commercially Reasonable Efforts to cause its Related Party to prepare written plans for each Licensed Compound (each a "**Karyopharm Development Plan**") setting forth the objectives of the Development to be conducted by Karyopharm and/or its Related Party with regard to such Licensed Compound and the Licensed Products containing such Licensed Compound in the Karyopharm Territory and written clinical development plans setting forth the Development activities and time tables regarding any Clinical Studies including Relevant Clinical Studies that Karyopharm and/or its Related Party conducts as of the Effective Date in the Karyopharm Territory or Karyopharm and/or its Related Party believes should be conducted within the Karyopharm Territory with regard to any Licensed Product. Within [**] after the Effective Date, Karyopharm shall prepare and submit to the JOC for review and discussion a Karyopharm Development Plan, which Karyopharm Development Plan shall be consistent with the Overview Plan and include a planning horizon of [**]. Karyopharm will present any proposed amendments to each Karyopharm Development Plan to the JOC for the JOC's review and discussion reasonably in advance of Karyopharm's intention to implement such plans or amendments. For each Karyopharm Development Plan, Karyopharm shall also prepare and submit an updated Karyopharm Development Plan to the JOC for the JOC's review and discussion [**].

2.5 Global Clinical Development Plan.

2.5.1 Global Clinical Development Plan. Karyopharm shall and/or shall use Commercially Reasonable Efforts to cause its Related Party to prepare written global clinical development plans setting forth the Development activities and time tables regarding any Global Clinical Study that Karyopharm and/or its Related Party believes should be conducted with regard to any Licensed Product (each a "**Global Clinical Development Plan**"). Within [**] after the Effective Date, Karyopharm shall prepare and submit to the JOC for review and approval, an initial Global Clinical Development Plan setting forth a plan for the conduct of Global Clinical Studies by or on behalf of Karyopharm or any of its

Related Parties relating to the applicable Licensed Products, the Development activities to be undertaken with respect to such Licensed Products by or on behalf of Karyopharm or any of its Related Parties in the Field and a time table for the conduct of such activities, which initial Global Development Plan shall be consistent with the Overview Plan and include a planning horizon of [**]. For each Global Clinical Development Plan, Karyopharm shall also prepare and submit an updated Global Clinical Development Plan to the JOC for the JOC's review and approval [**].

2.5.2 Global Clinical Studies.

(a) From time to time during the Term, either Karyopharm (and/or its Related Party) or Ono (and/or its Related Party) may submit to the JOC a proposal for a Global Clinical Study that would support the filing of an NDA for the Licensed Product with Regulatory Authorities in both the Karyopharm Territory and the Ono Territory (a "**Global Clinical Study Proposal**"). Each such Global Clinical Study Proposal shall include a draft synopsis, proposed timelines for the conduct of such Global Clinical Studies. The JOC shall review and approve each such Global Clinical Study Proposal. If the JOC approves a Global Clinical Study Proposal within [**] after the date of submission to the JOC of such Global Clinical Study Proposal, Karyopharm shall prepare a Global Clinical Development Plan based on such Global Clinical Study Proposal. The Parties shall discuss in good faith the applicable Global Clinical Development Plan through the Working Group designated by the JOC, if necessary and Karyopharm shall consider and reflect Ono's comments to such Global Clinical Development Plan to the extent that those comments are reasonable based on scientific, business, and/or other relevant considerations. Karyopharm shall provide such Global Clinical Development Plan for the JOC for review and approval. Ono shall be responsible for bearing all costs and expenses incurred for patients enrolled in such Global Clinical Study in the Ono Territory. In the event that the JOC does not approve the Global Clinical Study Proposal within [**] after such Global Clinical Study Proposal has been submitted to the JOC or the JOC does not approve the Global Clinical Development Plan within [**] after such Global Clinical Development Plan has been submitted to the JOC, such proposing Party shall be free to carry out at its own cost and expense the relevant Clinical Study(ies) described in such Global Clinical Study Proposal independently, within such proposing Party's Territory.

(b) If Karyopharm or its Related Party proposes to expand a then-existing clinical-stage Development effort including any Relevant Clinical Study and any Clinical Study in accordance with Karyopharm Development Plan so that it would become a Global Clinical Study, then Karyopharm shall include such proposal in a Global Clinical Development Plan and Karyopharm shall provide Ono with such Global Clinical Development Plan through the JOC and Working Group designated by the JOC for Ono's review. If Ono desires to participate in such Global Clinical Study, it shall provide written notice thereof to the JOC and Karyopharm within [**] after the date of the JOC's receipt of the applicable Global Clinical Development Plan. The Parties shall discuss the applicable Global Clinical Development Plan through the Working Group designated by the JOC during such [**] period if necessary, and Karyopharm shall consider and reflect Ono's comments to such Global Clinical Development Plan to the extent that those comments are reasonable based on scientific, business, and/or other relevant considerations. Karyopharm shall provide such Global Clinical Development Plan to the JOC for review and approval. Ono shall be responsible for bearing all costs and expenses incurred for patients enrolled in such Global Clinical Study in the Ono Territory after the date of JOC's approval.

(c) If Ono notifies Karyopharm in writing that Ono reasonably believes that a Clinical Study of a Licensed Product in the Field being conducted or determined to be conducted by Karyopharm and/or its Related Party in accordance with Karyopharm Development Plan or proposed by Karyopharm and/or its Related Party should be expanded to be a Global Clinical Study, Karyopharm shall expand such Clinical Study into a Global Clinical Study, and Karyopharm will include such proposal in a Global Clinical Development Plan that it provides to Ono through the JOC and Working Group designated by the JOC for the JOC's review within [**] after the date of Karyopharm's receipt of Ono's written notification. The Parties shall discuss in good faith the applicable Global Clinical Development Plan through the Working Group designated by the JOC during such [**] period if necessary, and Karyopharm shall consider and reflect Ono's comments to such Global Clinical Development Plan to the extent that those comments are reasonable based on scientific, business, and/or other relevant considerations. Karyopharm shall provide such Global Clinical Development Plan to the JOC for review and approval. Ono shall be responsible for bearing all costs and expenses incurred for patients enrolled in such Global Clinical Study in the Ono Territory after the date of JOC's approval.

(d) In connection with any Global Clinical Development Plan or amendment thereto that includes any Global Clinical Study, Karyopharm may present comments on such Global Clinical Development Plan or amendment thereto from any Karyopharm's Related Party outside of the Ono Territory with regard to the conduct of any such Global Clinical Study and the JOC shall consider in good faith any such comments.

(e) In case that amendment to the Global Clinical Development Plan is finally decided as the result of Karyopharm's exercise of its deciding vote pursuant to Section 5.4.3(b), Ono may change the status of its part therein from "Global Clinical Study" to "Development in the Ono Territory", which will be subject to Ono's final deciding vote set forth in Section 5.4.3(a).

2.6 Responsibilities for Development Activities and Costs; No Conduct in Other Party's Territory.

2.6.1 Ono Development Activities. Ono shall be responsible for the Development of the Licensed Products for each Licensed Compound in the Field in the Ono Territory, including the conduct of any Clinical Studies in the Ono Territory, in accordance with the terms of this Agreement. Ono shall be responsible for one hundred percent (100%) of all costs and expenses relating to Development activities that are conducted by or on behalf of Ono, including Global Clinical Studies in the Ono Territory. Ono will conduct all Development of the Licensed Products in the Field for the Ono Territory solely in accordance with the terms of this Agreement and the applicable Ono Development Plan or Global Clinical Development Plan, as applicable, as such Ono Development Plan or Global Clinical Development Plan may be amended or updated from time to time in accordance with this Agreement, and in accordance with all applicable Law.

2.6.2 **Karyopharm Development Activities**. Karyopharm shall be responsible for, at its own cost and expense, all of its activities relating to the Development of the Licensed Compounds and the Licensed Products in the Karyopharm Territory and Global Common Activity, including the costs and expenses relating to its participation in Global Clinical Studies in the Karyopharm Territory or to conduct additional Development work in the Karyopharm Territory to Develop a Back-Up Compound. In addition, Karyopharm shall be responsible for all of its own costs and expenses relating to the preparation of any Global Clinical Study Plan and all Global Common Costs. "**Global Common Activity**" means any Development activity with regard to Global Clinical Study that is not specific to Development activities in Ono Territory or Karyopharm Territory: which includes, but not limited to, the project management, data management, pharmacovigilance support, statistical support and statistical analysis on global basis (i.e. both of Karyopharm Territory and Ono Territory).

2.6.3 **No Conduct of Clinical Trials in Other Party's Territory**. During the Term, neither Party may conduct Clinical Studies or other Development activities with respect to a Licensed Product in the other Party's Territory without such other Party's prior written consent, which consent may be granted or withheld in the sole discretion of the other Party.

2.7 **Development in the Ono Territory.**

2.7.1 **Diligence**. With respect to each Licensed Compound, Ono will use Commercially Reasonable Efforts to Develop and to obtain Regulatory Approval for the Licensed Products in the Field in each country in the Ono Territory.

2.7.2 **Amendment to Ono Development Plan Subsequent to Discontinuation of the Development of a Licensed Product**. In the event that Ono determines not to continue the Development of a Licensed Product in the Field in the Ono Territory, Ono shall notify the JOC of its discontinuation of such Development activities in a written statement, which describes in reasonable detail the reasons that Ono determined to discontinue such Development activities. Karyopharm shall provide the JOC with all Know-How on all candidates for Back-Up Compounds Controlled by Karyopharm or its Affiliates as soon as practicable after its receipt through JOC of such notification by Ono. The Parties, through JOC, shall use Commercially Reasonable Efforts to determine a Back-Up Compound among such candidates (or not to select a Back-Up Compound), which replaces a Licensed Compound. Ono shall prepare an amendment to the Ono Development Plan to reflect any changes to the objectives, Development activities or time table set forth in the Ono Development Plan arising from the replacement of such discontinued Licensed Product with a substitute Licensed Product, if any, within [**] after the determination of Back-Up Compound by the JOC.

2.8 **Records; Reports; Information Sharing.**

2.8.1 Development Activities. Each Party will provide the JOC with a [**] update regarding Development activities conducted by or on behalf of each Party and/or its Related Party under this Agreement. Each Party shall regularly inform the other Party, and shall formally provide written progress reports for the JOC on a [**] basis, summarizing the Development activities conducted by each Party and its Related Party, including any issues relating to meeting the obligations, objectives or timetables set forth each in the Ono Development Plan, the Karyopharm Development Plan or the Global Development Plan.

2.8.2 Scientific Records. Subject to Section 7.1.3, each Party shall and shall use Commercially Reasonable Efforts to cause its Related Party to maintain complete, current and accurate records of all Development work conducted by or on behalf of each Party and/or its Related Party, and all Clinical Data, Data and other Know-How resulting from such work. Such records shall fully and properly reflect all work done and results achieved in the performance of the Development activities in a good scientific manner appropriate for regulatory and patent purposes. Each Party shall, and shall use Commercially Reasonable Efforts to cause its Related Party to, document all Clinical Studies and other studies and research in formal written study reports in accordance with applicable guidelines (*e.g.*, GCP, GLP, and GMP) and all other applicable Law. Subject to 7.1.3, each Party shall, and shall use Commercially Reasonable Efforts to cause its Related Party, to make all such Clinical Data, records and reports continuously available, within a reasonable period following their creation, to the other Party for inspection and review (including, to the extent reasonably requested, copying) through appropriate electronic data room facilities. Subject to applicable Law (including, but not limited to, the data privacy act in each country), each Party shall also have the right to review original versions of such records maintained by other Party and its Affiliates (and, to the extent permissible, its Related Parties) no more often than [**], at reasonable times, upon written request to other Party.

2.8.3 Data Transfer.

(a) Within [**] after the Effective Date, Karyopharm shall transfer in electronic format to Ono all technical, and regulatory documents and Data Controlled by Karyopharm that are necessary or useful for Ono to conduct the Development activities and to perform Ono's obligation or exercise Ono's rights hereunder, existing as of the Effective Date. The Parties acknowledge that Karyopharm may be requested to arrange notarization or other certification of certain elements of the Data of Karyopharm and its Affiliates for official purposes. With Ono's guidance or to the extent required for Development as requested by Regulatory Authorities for the Licensed Products in the Ono Territory, Karyopharm shall provide Ono with copies of documents covering (i) Data authenticity documents relevant to the Licensed Compounds and Licensed Products, (ii) authorization to use Data provided by Karyopharm, (iii) documentation perfecting the patent license provisions of this Agreement, and (iv) GLP documents; provided, however, that the foregoing shall reflect Karyopharm's work conducted prior to the Effective Date and none of the foregoing shall require Karyopharm to perform or conduct further research, laboratory, Manufacturing or other work solely for the Ono Territory,

including any work to establish GLP or GMP compliance, except pursuant to Section 2.8.3(b) below. Karyopharm's provision of those documents shall be made in accordance with the time-schedule agreed upon between the Parties (to the extent feasible, within [**] after the Effective Date).

(b) If Ono believes it would be desirable to have additional work performed by Karyopharm to assist in the transition of Development activities from Karyopharm to Ono or an on-site transfer, the Parties may jointly develop a written scope of work to be performed by Karyopharm and Ono, including timelines, terms, costs, and resource requirements, to be mutually agreed by both Parties. The JOC will review and provide comments on any such scope of work before such scope of work is executed by both Parties. Out-of-pocket costs incurred by the Parties for such additional work shall be [**].

2.8.4 Information Sharing. During the Term, subject to Section 7.1.3, each Party shall provide the other Party with all Know-How Controlled by such Party and/or use Commercially Reasonable Efforts to provide the other Party with all Know-How Controlled by its Related Party, that is generated during the Term of this Agreement, that has not previously been provided hereunder and that is necessary or useful for the Development or Commercialization of the Licensed Compounds or Licensed Products in the Field in the other Party's Territory, in each case promptly upon request by the other Party. The Party providing such Party's and/or its Related Party's Know-How shall provide the same in electronic form to the extent the same exists in electronic form, and shall provide copies for all other materials comprising such Know-How (including, for example, original patient report forms and other original source data). Any Data provided by one Party to the other Party under this Section 2.8.4 shall be provided in the original language in which such Data was generated, provided that, with respect to Data relating to any Global Clinical Study, if such original language is not English, then the Party supplying such Data shall also provide English translations thereof and the expense for such English translations shall be [**]. The Parties will cooperate and reasonably agree upon formats and procedures to facilitate the orderly and efficient exchange of such Know How.

2.8.5 Rights of Reference and Access to Data. Subject to Section 7.1.3, each Party shall have the right to cross-reference the regulatory filings and Regulatory Approvals (and each Party's Related Party's regulatory filings and Regulatory Approvals) related to the Licensed Products, and to access such regulatory filings and such Regulatory Approvals and any Data therein and use such Data in connection with the performance of its obligations and exercise of its rights under this Agreement, including inclusion of such Data in its own regulatory filings for a Licensed Product free of charge. Each Party hereby will grant, and will cause its Related Party to grant, to the other Party and its Related Party a "Right of Reference," as that term is defined in 21 C.F.R. § 314.3(b) in the United States, or an equivalent right of access/reference in any other country or region, to any Data, including such Party's or its Related Party's clinical dossiers, Controlled by such Party or such Related Party that relates to the Licensed Product for use by the other Party to Develop and Commercialize the Licensed Product in

the Field pursuant to this Agreement. Each Party shall provide a signed statement to this effect, if requested by the other Party, in accordance with 21 C.F.R. § 314.50(g)(3) or the equivalent as required in any country or region or otherwise provide appropriate notification of such right of the other Party to the applicable Regulatory Authority and shall cause its Related Party to provide such signed statement. Each Party will provide, and will cause its Related Party to provide, cooperation to the other Party to effect the foregoing.

2.8.6 Investigator Sponsored Clinical Studies. Ono shall have the right to authorize the protocol for each Investigator Sponsored Clinical Study in the Ono Territory and support such Investigator Sponsored Clinical Study at Ono's own discretion, provided, however, Ono agrees to inform Karyopharm of all such Investigator Sponsored Clinical Study(ies) in a timely manner and each proposal shall be subject to review and comment by a Working Group designated by the JOC. Karyopharm shall have the right to authorize the protocol for each Investigator Sponsored Clinical Study in the Karyopharm Territory and support such Clinical Study at Karyopharm's own discretion, provided, however, Karyopharm agrees to inform Ono of all such Investigator Sponsored Clinical Study(ies) in a timely manner and each proposal shall be subject to review and comment by a Working Group designated by the JOC. Neither Party shall authorize or support an Investigator Sponsored Clinical Study in the other Party's Territory without such other Party's prior written consent, which consent may be granted or withheld in the sole discretion of the other Party.

3. REGULATORY MATTERS

3.1 Regulatory Filings and Interactions.

3.1.1 Responsibilities. Each Party will own the INDs, the NDAs and related regulatory documents submitted to the applicable Regulatory Authorities for its Development activities with respect to each Licensed Product in the Field, and for Commercialization in its Territory with respect to each Licensed Product in the Field. Each Party will (a) oversee, monitor and coordinate all regulatory actions, communications and filings with, and submissions to, each Regulatory Authority, (b) be responsible for interfacing, corresponding and meeting with each Regulatory Authority and (c) be responsible for maintaining all regulatory filings, in each case of (a)-(c) with respect to its Development activities with respect to each Licensed Product in the Field, and with respect to Commercialization of each Licensed Product in the Field in its Territory.

3.1.2 Communications and Cooperation. Karyopharm shall cooperate in good faith with Ono pertaining to Ono's Development activities and regulatory affairs with respect to each Licensed Product in the Field in the Ono Territory at Ono's sole cost and expense. Ono will, as to each Licensed Product in the Field in the Ono Territory, (a) notify Karyopharm in writing of all material communications from a Regulatory Authority within [**] after receipt thereof, including a brief description in English of the principal issues raised, (b) provide

Karyopharm with a summary translation of such material communications in English as soon as reasonably possible, and (c) provide the complete copies of the original correspondence in its original language to Karyopharm upon request. Ono shall provide Karyopharm with reasonable advance notice of all substantive meetings with the Regulatory Authorities in the Ono Territory pertaining to each Licensed Product in the Field, or with as much advance notice as practicable under the circumstances. Karyopharm may, at its own cost, attend such meetings with Regulatory Authorities as an observer upon reasonable advance notice to Ono, subject to Ono's prior written consent and receipt of any required permissions of such Regulatory Authorities. Karyopharm will, as to each Licensed Product in the Field in the Karyopharm Territory, (a) notify Ono in writing of all material communications from a Regulatory Authority within [**] after receipt thereof, including a brief description in English of the principal issues raised, (b) provide Ono with a summary translation of such material communications in English as soon as reasonably possible, and (c) provide the complete copies of the original correspondence in its original language to Ono upon request. Karyopharm shall provide Ono with reasonable advance notice of all substantive meetings with the Regulatory Authorities in the Karyopharm Territory pertaining to each Licensed Product in the Field, or with as much advance notice as practicable under the circumstances. Ono may, at its own cost, attend such meetings with Regulatory Authorities as an observer upon reasonable advance notice to Karyopharm subject to Karyopharm's prior written consent and receipt of any required permissions of such Regulatory Authorities.

3.1.3 Without limiting the obligations under Section 3.1.2, Ono shall provide to Karyopharm copies of the proposed labeling for the Licensed Product in the local language to be filed in the Ono Territory. Additionally, Ono shall provide Karyopharm with (a) a copy of the NDA in electronic format, provided that in cases where the NDA was not filed electronically, Ono will provide the electronic files used to generate such submission, and (b) copies of the final labeling for the Licensed Product in the local language in all countries in the Ono Territory in which Ono obtains Regulatory Approvals. Karyopharm shall and/or shall cause its Related Party to provide Ono with copies of the proposed labeling for the Licensed Product in the local language to be filed by Karyopharm in United States, France, Germany, Italy, Spain and the United Kingdom. Additionally, (a) Karyopharm shall, and shall cause its Related Party, to provide Ono with a copy of the NDA filed by Karyopharm and/or its Related Party with the FDA and the EMA, in each case in electronic format, provided that in cases where the NDA was not filed electronically, Karyopharm will and/or will cause its Related Party to provide the electronic files used to generate such submission, and (b) Karyopharm shall and/or shall cause its Related Party to provide Ono with copies of the final labeling for the Licensed Product in the local language in all countries in the Karyopharm Territory in which Karyopharm and/or its Related Party obtain(s) Regulatory Approvals.

3.1.4 Submissions. In addition, Ono shall provide the JOC with written notice of the fact of (a) the filing and submitting for Regulatory Approval (including orphan drug applications and designations) regarding each Licensed Product in the Field in the Ono Territory in a timely manner; (b) whether Regulatory Approval is obtained or denied regarding each Licensed Product in the Field in the Ono Territory in a timely manner; and (c) the filing of any IND for each Licensed Product in the Field in the Ono Territory as soon as practicable after such event; provided, however, that in all circumstances, Ono shall inform the JOC of such event prior to public disclosure of such event by Ono except to the extent such public disclosure is required by Law.

3.2 Costs of Regulatory Affairs. Each Party shall be responsible for all costs incurred by or on behalf of it in connection with applying for Regulatory Approval with respect to each Licensed Product in the Field in each country in its own Territory and related regulatory affairs activities.

3.3 Pharmacovigilance. Prior to Ono's filing IND for its first Clinical Study with respect to the Licensed Products, the Parties will negotiate and finalize a Safety Data Exchange Agreement (the "**SDEA**") to be agreed upon in writing, that will define the pharmacovigilance responsibilities of the Parties and include safety data exchange procedures governing the coordination of collection, investigation, reporting, and exchange of information concerning any adverse experiences, and any product quality and product complaints associated with adverse experiences, related to the Licensed Products, sufficient to enable each Party (and their respective Related Parties, if any) to comply with its legal and regulatory obligations. The SDEA shall be modified in writing before obtaining the Regulatory Approval for such Licensed Products in either Territory, to enable each Party (and their respective Related Parties, if any) to comply with its legal and regulatory obligations. The Parties shall use Commercially Reasonable Efforts to amend the SDEA to add as parties any Related Parties.

4. COMMERCIALIZATION OF THE LICENSED PRODUCTS

4.1 Responsibility, Cost and Diligence.

4.1.1 Ono's Commercialization Activities. Subject to the terms of this Agreement, Ono shall be solely responsible for all Commercialization activities relating to the Licensed Products in the Field in the Ono Territory. Ono shall be responsible for one hundred percent (100%) of all costs relating to Commercialization activities that are conducted by or on behalf of Ono. With respect to each Licensed Compound, Ono shall use Commercially Reasonable Efforts to Commercialize the Licensed Products in the Field in each country within the Ono Territory (including obtaining all required pricing and reimbursement approvals) as promptly as possible following receipt by Ono or its Related Parties of Regulatory Approval for such Licensed Product in such country. Such Commercialization efforts may include conducting Ono post-registration studies in the Ono Territory as may be necessary to expand the potential market for Licensed Products in the Field, planning and implementation, distribution, booking of sales, pricing and reimbursement, establishing and developing appropriate opinion leaders, promoting Licensed Products with managed care organizations and establishing Licensed Products with formularies.

4.1.2 Karyopharm's Commercialization Activities. Karyopharm shall be responsible for, at its own cost and expense, all of its activities relating to Commercialization of the Licensed Products in the Karyopharm Territory, including planning and implementation, distribution, booking of sales, pricing and reimbursement.

4.2 Reporting Obligations. Ono shall provide Karyopharm with written notice of each First Commercial Sale of a Licensed Product in a country in the Ono Territory within [**] after such event; provided, however, that in all circumstances, Ono shall inform Karyopharm of such event prior to public disclosure of such event by Ono. Ono shall also provide such other information, including its sales department structure, sales marketing structure and medical affairs structure to the JOC as Ono deems necessary or useful for Karyopharm and shall keep Karyopharm and the JOC reasonably informed of Ono's Commercialization activities with respect to Licensed Products.

4.3 Commercialization by Karyopharm. Karyopharm shall provide information regarding its Commercialization activities, including its sales department structure, sales marketing structure and medical affairs structure to the JOC as Karyopharm deems necessary or useful for Ono and shall keep Ono and the JOC reasonably informed of Karyopharm's Commercialization activities with respect to Licensed Products.

4.4 Sales and Distribution. Each Party and its Related Parties shall be responsible for booking sales and shall warehouse and distribute Licensed Products in the Field in its Territory. Moreover, each Party and its Related Parties shall be solely responsible for handling all returns of Licensed Product in the Field sold in its Territory, as well as all aspects of Licensed Product order processing, invoicing and collection, distribution, inventory and receivables of Licensed Products sold in its Territory.

4.5 Recalls, Market Withdrawals or Corrective Actions. In the event that any Regulatory Authority issues or requests a recall or market withdrawal or takes a similar action in connection with the Licensed Product in the Field in any part of a Party's Territory, or in the event either Party determines that an event, incident or circumstance has occurred that may result in the need for such a recall, market withdrawal or similar action in its own Territory, the Party notified of such a recall, market withdrawal or similar action, or the Party that desires such a recall, market withdrawal or similar action, shall within [**] advise the other Party thereof by telephone, facsimile or e-mail, followed immediately by a notice in accordance with Section 14.10. Each Party, in consultation with the other Party but in its own discretion, shall decide whether to conduct such a recall, market withdrawal or similar action in its own Territory and the manner in which any such a recall, market withdrawal or similar action shall be conducted (except in the case of a government mandated recall, market withdrawal or similar action when such Party may act without such advance notice but shall notify the other Party as soon as possible). Subject to the terms and conditions of the Supply Agreement, each Party shall bear the expense of any such a recall, market withdrawal or similar action in its own Territory. Each Party will make available all of its pertinent records that may be reasonably requested by the other Party in order to effect such a recall, market withdrawal or similar action in the other Party's Territory.

4.6 Ex-Territory Sales; Export Monitoring.

4.6.1 Ex-Territory Sales. Subject to applicable Law, neither Party shall engage in any advertising or promotional activities relating to any Licensed Product in the Field directed primarily to customers or other buyers or users of such Licensed Product in the Field located outside its Territory or accept orders for such Licensed Product in the Field from, or sell such Licensed Product in the Field into, such other Party's Territory for its own account, and if a Party receives any order for such Licensed Products in the Field in the other Party's Territory, it shall refer such orders to the other Party.

4.6.2 Export Monitoring. Each Party and its Related Parties will use Commercially Reasonable Efforts at its own cost to monitor and prevent exports of each Licensed Product from its own Territory for Commercialization in the other Party's Territory, or commercial use in the Ono Territory outside the Field of a Licensed Product sold by Ono or its Related Parties, using methods commonly used in the industry for such purpose, and shall promptly inform the other Party of any such exports of any Licensed Product from its Territory of which it becomes aware, and the actions taken to prevent such exports, to the extent permitted by applicable Law. Each Party shall, at the other Party's cost, take reasonable actions requested in writing by the other Party that are consistent with applicable Law to prevent exports of the Licensed Products from its Territory for Commercialization in the other Party's Territory or the use of Licensed Product, to the extent permitted by applicable Law.

4.7 Promotional Materials.

4.7.1 Karyopharm Promotional Materials. Subject to Section 7.1.3, Karyopharm shall, and shall use Commercially Reasonable Efforts to cause its Related Party to, provide Ono with copies of core promotional materials (written, printed, video or graphic advertising, promotional, educational and communication materials) developed and used in the Karyopharm Territory by Karyopharm or its Related Parties in Commercializing the Licensed Product to support Ono's Commercialization activities for the Licensed Product in the Ono Territory, including materials relating to marketing strategies for the Licensed Product in the Karyopharm Territory pursued by Karyopharm or its Related Parties, where reasonably requested by Ono. Ono may use information contained in such promotional materials, free of charge, for preparation of promotional materials relating to the Licensed Product for use by Ono or its Related Parties in connection with Commercialization of the Licensed Product in the Field in the Ono Territory and for no other purpose, unless the Parties agree otherwise in writing.

4.7.2 Ono Promotional Materials. Subject to Section 7.1.3, Ono shall, and shall use Commercially Reasonable Efforts to cause its Related Parties to, provide Karyopharm with copies of core promotional materials (written, printed, video or graphic advertising, promotional, educational and communication materials) developed and used in the Ono Territory by Ono or its Related Parties in Commercializing the Licensed Product to support Karyopharm's Commercialization activities for the Licensed Product in the Karyopharm Territory, including materials relating to marketing strategies for the Licensed Product in the Ono Territory pursued by Ono or its Related Parties, where reasonably requested by Karyopharm. Karyopharm may use information contained in such promotional materials, free of charge, for preparation of promotional materials relating to the Licensed Product for use by Karyopharm or its Related Parties in connection with Commercialization of the Licensed Product in the Karyopharm Territory and for no other purpose, unless the Parties agree otherwise in writing.

5. GOVERNANCE.

5.1 Joint Operating Committee. Within [**] after the Effective Date, Karyopharm and Ono shall designate their representatives to the joint operating committee (the "**Joint Operating Committee**" or "**JOC**") to oversee and monitor Development, Manufacturing, use and Commercialization activities, and to serve as the decision-making body for certain activities, under this Agreement with respect to the Licensed Compounds and the Licensed Products in the Field. The Parties anticipate that the JOC will not be involved in day-to-day implementation of such activities under this Agreement.

5.1.1 Composition of the Joint Operating Committee. The JOC shall be comprised of an equal number of representatives of each Party, which number shall be three (3) representatives of each Party. The JOC representatives shall be senior-level employees of the appointing Party having appropriate experience, expertise and decision-making authority. All JOC representatives shall have appropriate expertise and ongoing familiarity with the Licensed Products in the Field and this Agreement. Either Party may replace its respective JOC representatives at any time with prior written notice to the other Party; provided that the criteria for composition of the JOC set forth in the preceding sentence shall continue to be satisfied following any such replacement of a Party's representative on JOC. An alternate member designated by a Party may serve temporarily in the absence of a member of the JOC for such Party. Each Party may invite its employees involved in Development, Manufacturing, use or Commercialization of the Licensed Product for JOC meetings with the prior notice to the other Party. All representatives on the JOC, and all other attendees at a JOC meeting, shall be subject to confidentiality obligations, whether in a written agreement or by operation of law, no less stringent than the requirements of Section 9.1.

5.1.2 JOC Responsibilities. The JOC shall have the following responsibilities:

(a) review and discuss each Ono Development Plan, and all amendments and updates to such Ono Development Plan;

(b) as part of its review and discussion of an Ono Development Plan, take into account the comments or views of Karyopharm or any of Karyopharm's Related Parties outside of the Ono Territory as Karyopharm may present to the JOC;

(c) review progress reports provided by Ono with respect to its Development activities;

(d) monitor and provide Ono with feedback regarding the conduct of Development activities by or on behalf of Ono;

(e) review and discuss each Karyopharm Development Plan, and all amendments and updates to such Karyopharm Development Plan;

(f) review progress reports provided by Karyopharm with respect to Development activities by Karyopharm and its Related Party;

(g) coordinate Development activities conducted by Ono and its Related Parties with the activities conducted by Karyopharm and its Related Parties in their respective Territories, including regulatory and pharmacovigilance requirements and matters;

(h) subject to the escalation provision in Section 5.4, review and approve each Global Clinical Study Proposal (it being confirmed that such review shall be subject to and supported by information sharing exchange in the Global Development Working Group pursuant to Section 5.5);

(i) subject to the escalation provision in Section 5.4, review and approve each Global Clinical Development Plan and any amendments to such Global Clinical Development Plan (it being confirmed that such review shall be subject to and supported by information sharing exchange in the Global Development Working Group pursuant to Section 5.5);

(j) review and discuss each Party's and/or its Related Party's long term Development strategy in the respective Territory in a timely manner (it being confirmed that such review and discussion shall be subject to and supported by information sharing exchange in the Global Development Working Group pursuant to Section 5.5);

(k) designate a Back-Up Compound among its candidates provided by Karyopharm in accordance with Section 2.7.2;

(l) review and provide comments on scope of work for additional work relating to Data transfer as specified in Section 2.8.3(b);

(m) oversee the manufacturing and supply relationship between the Parties with respect to Manufacture of Licensed Compounds and Licensed Products in case Licensed Compounds and Licensed Products are supplied by the Karyopharm to Ono for the Ono Territory;

(n) review and provide comments with respect to the commercialization plan and marketing strategy of Karyopharm and/or any of Karyopharm's Related Party in the Karyopharm Territory and Ono and/or any of Ono's Related Party in the Ono Territory and any material updates or amendments thereto;

(o) providing a forum for the Parties to discuss Commercialization of Licensed Products in the Field worldwide, including coordination regarding Licensed Product positioning and messaging, key opinion leader relationship management, medical affairs, and marketing and selling materials; and

(p) performing such other activities as the Parties shall determine to be the responsibility of the JOC.

5.1.3 **JOC Chairperson.** Each Party shall designate one (1) of their JOC representative to be a co-chairperson. The JOC shall be co-chaired by one (1) representative selected by Karyopharm and one (1) representative selected by Ono (the "**JOC Chairpersons**"). Either Party shall have the right to change their JOC Chairperson by written notice to the other Party. The JOC Chairpersons' responsibilities shall include (a) scheduling meetings in accordance with Section 5.2.1, but more frequently if a Party request in accordance with Section 5.2.1 or the JOC determines it necessary; (b) setting agendas for meetings with solicited input from other members; (c) coordinating the delivery of draft minutes to the JOC for review and final approval; and (d) conducting meetings, including ensuring that objectives for each meeting are set and achieved.

5.2 Meetings.

5.2.1 The JOC shall meet no less frequently than [**] until the [**] and [**] during the Term. In addition to the regular meetings, either Party may request an ad-hoc meeting of the JOC to solve any specific issues from time to time. In the event that an urgent issue or matter that requires prompt action by the JOC arises, each Party may call an emergency meeting of the JOC to attempt to resolve such issue or matter. Such meeting (or other means of communication) shall take place by teleconference or videoconference (unless otherwise mutually agreed by the Parties) as promptly as possible.

5.2.2 The location for the in-person meetings of the JOC shall, respectively, alternate between Karyopharm's headquarters and Ono's headquarters (or such other locations as are mutually agreed by the Parties). Alternatively, the JOC may meet by means of teleconference, videoconference or other similar communications equipment, but at least [**] of the JOC shall be conducted in person.

5.2.3 All proceedings for the JOC shall take place in English. Each Party shall bear its own expenses relating to participation at such meetings by its representatives.

5.3 **Minutes**. The Liaison of a Party who is hosting the meeting (in person or via teleconference, videoconference or other similar communications equipment) shall arrange each meeting of the JOC and shall prepare minutes of the meeting, which shall provide a description in reasonable detail of the discussions held at the meeting and a list of any actions, decisions or determinations approved by the JOC.

5.4 **Decision-Making.**

5.4.1 Any decisions of the JOC shall be made by unanimous vote. With respect to decisions of the JOC, each Party shall have one (1) vote, exercised through its representatives on the JOC on behalf of such Party. For each meeting of the JOC, a quorum exists so long as there is at least one (1) representative of each Party present at the meeting. Action on any matter may be taken at a meeting, by teleconference, videoconference or by written consent. The JOC shall attempt to resolve any and all disputes before it for decision by consensus.

5.4.2 If the JOC is unable to reach unanimous agreement after working in good faith to reach a consensus and taking into account all reasonable medical, scientific, and clinical considerations and considering each Party's comments or requests on such matters that would adversely impact the safety, commercial value or reputation of the Licensed Products, with respect to a dispute relating to a JOC responsibility described in Section 5.1.2 other than those set forth Sections 5.1.2(h) and 5.1.2(i) for a period in excess of [**], then the dispute shall be submitted to the Executive Officers for resolution. If the JOC is unable to reach unanimous agreement after working in good faith to reach a consensus and taking into account all reasonable medical, scientific, and clinical considerations and considering each Party's comments or requests on such matters that would adversely impact the safety, commercial value or reputation of the Licensed Products, with respect to a dispute relating to a JOC responsibility set forth Sections 5.1.2(h) or 5.1.2(i) for a period in excess of [**], then the dispute shall be reviewed by a Working Group (as defined below) designated by the JOC, which shall within [**] submit to the JOC a written analysis of the dispute and recommendations for resolving the dispute. If the Working Group fails to timely submit such analysis and recommendations or if the JOC is unable to reach unanimous agreement with respect to such dispute for a period in excess of [**] following the receipt of such analysis and recommendation, then the dispute shall be submitted to the Executive Officers for resolution.

5.4.3 If such dispute cannot be resolved for a period in excess of [**] following the escalation to the Executive Officers, then, such dispute shall be subject to this Section 5.4.3:

(a) Subject to Section 5.4.4 and 5.4.5, Ono shall have the deciding vote with respect to any aspects of such matter relating to the Ono Territory, including the Ono Development Plan; provided that, any and all deciding votes shall be in good faith, and after good faith consideration of Karyopharm's comments or requests on such matters that would adversely impact the safety, commercial value or reputation of the Licensed Products, and with due regard for the impact of such deciding vote on Development and Commercialization of the Licensed Products in the Karyopharm Territory and consistency in all material respects with the terms of this Agreement.

(b) Subject to Section 5.4.4 and 5.4.5, Karyopharm shall have the deciding vote with respect to any aspects of such matter relating to the Karyopharm Territory, as well as any amendment to a Global Clinical Development Plan; provided that, any and all deciding votes shall be in good faith, and after good faith consideration of Ono's comments or requests on such matters that would adversely impact the safety, commercial value or reputation of the Licensed Products, and with due regard for the impact of such deciding vote on Development and Commercialization of the Licensed Products in the Ono Territory and consistency in all material respects with the terms of this Agreement.

5.4.4 Neither Party shall have the deciding vote on, and the JOC shall not have decision-making authority regarding, any of the following matters, which shall be mutually agreed to by the Parties:

(a) any matter that would materially adversely impact the safety, commercial value or reputation of a Licensed Product in the Ono Territory;

(b) the imposition of any requirements on the other Party to undertake obligations beyond those for which it is responsible, or to forgo any of its rights, under this Agreement;

(c) the imposition of any requirements that the other Party take or decline to take any action that would result in a violation of any Law or any agreement with any Third Party or the infringement of intellectual property rights of any Third Party;

(d) any matters that would excuse such Party from any of its obligations under this Agreement; or

(e) modifying the terms of this Agreement or taking any action to expand or narrow the responsibilities of the JOC.

5.4.5 Notwithstanding anything to the contrary set forth herein,

(a) the decision-making Party shall make its decision in good faith, subject to the terms and conditions of this Agreement;

(b) in no event may the decision-making Party unilaterally determine that it has fulfilled any obligations hereunder or that the non-deciding Party has breached any obligations hereunder; and

(c) Ono may not make a decision that would cause Karyopharm to be in breach of a provision of a Karyopharm Third Party Agreement.

5.5 Working Groups. Upon mutual agreement, the Parties may establish other committees or working groups (each, a "**Working Group**") as they deem appropriate. These Working Groups shall report to the JOC depending on the subject matter of such Working Group's oversight. Each Working Group shall have equal number of representatives from each Party. Working Group may be established on an ad hoc basis for purposes of a specific project. In no event shall the authority of a Working Group exceed that of the JOC. The Parties agree to the establishment of a joint intellectual property working group (the "**IP Working Group**") and a global development working group (the "**Global Development Working Group**") after the Effective Date. The IP Working Group shall (a) review and discuss intellectual property matters relating to a Licensed Compound or Licensed Product in the Field, and (b) in the case of Joint IP, determining which Party shall be the Joint IP Prosecuting Party for such Joint IP. The Global Development Working Group shall use Commercially Reasonable Effort to share and exchange enough information on such matters in advance of the JOC so that the JOC members may make enough preparation and have discussion in efficient and effective manner.

5.6 Liaisons. Within [**] following the Effective Date, each Party shall appoint a representative ("**Liaison**") to facilitate communications between the Parties (including, coordinating the exchange of Data and Know-How of each Party as required under this Agreement) and to act as a liaison between the Parties with respect to such other matters as the Parties may mutually agree in order to maximize the efficiency of the collaboration. Each Party may replace its Liaison with an alternative representative at any time with prior written notice to the other Party. Each Party's Liaisons shall be entitled to attend all JOC meetings. Each Liaison may bring any matter to the attention of the JOC where such Liaison reasonably believes that such matter requires attention of the JOC. Each Liaison shall be responsible with creating and maintaining a collaborative work environment within the JOC.

5.7 Authority. The JOC will have only the powers assigned expressly to it in this Article 5, and will not have any power to amend or modify the terms of this Agreement or waive compliance with this Agreement. In furtherance thereof, each Party will retain the rights, powers and discretion granted to it under this Agreement and no such rights, powers or discretion will be delegated to or vested in the JOC unless such delegation or vesting of rights is expressly provided for in this Agreement or the Parties expressly so agree in writing.

5.8 Committee involving Karyopharm's Related Party. In the case a Related Party of Karyopharm is responsible for Development and/or Commercialization of License Compound and Licensed Product in the United States, France, Germany, Italy, Spain and/or the United Kingdom, upon Ono's request, Karyopharm shall use Commercially Reasonable Efforts to arrange and establish a committee constituted by representatives of Karyopharm, such Related Party and Ono to oversee and monitor Development and/or Commercialization of the Licensed Compound and Licensed Product on global basis.

6. MANUFACTURE AND SUPPLY

6.1 Clinical Supply.

6.1.1 **Clinical Supply**. Subject to Section 6.2.3, Karyopharm shall use Commercially Reasonable Efforts to Manufacture and supply all quantities of the Licensed Compounds and/or Licensed Products for use by Ono in the Development of Licensed Products in the Ono Territory, including to obtain Regulatory Approval in the Ono Territory. It is confirmed that, as Karyopharm's Commercially Reasonable Efforts set forth in this Section, Karyopharm shall supply to Ono [**] tablets of selinexor as initial requirement for Development in the Ono Territory within [**] from the Effective Date and subsequent requirements of clinical supplies for Development in the Ono Territory pursuant to the terms and conditions of the Clinical Supply Agreement. Ono's purchase price for the Licensed Compounds and Licensed Products shall be [**].

6.1.2 **Clinical Supply Agreement**. The Manufacturing and supply by Karyopharm of the Licensed Compounds and Licensed Products for Development purposes shall be governed by a mutually acceptable clinical supply agreement (the "**Clinical Supply Agreement**") and a mutually acceptable clinical quality agreement (the "**Clinical Quality Agreement**") which shall include the terms and conditions as are reasonable and customary for an agreement governing the Manufacturing and supply of compounds and products similar to the Licensed Compounds and the Licensed Products for clinical supply purposes. The Clinical Supply Agreement and Clinical Quality Agreement shall be finalized within [**] period after the Effective Date. In no event shall Karyopharm be obligated to supply quantities of Licensed Compounds and/or Licensed Products in excess of amounts reasonably necessary to satisfy Ono's and its Related Party's Development requirements in the Field in the Ono Territory.

6.2 **Commercial Supply.**

6.2.1 **Commercial Supply**. With respect to supply of each of the Licensed Products for Commercialization, in the case Ono does not elect to Manufacture the Licensed Compounds and/or Licensed Products by itself, Ono may purchase all of its requirements for the Licensed Compounds and/or Licensed Products for the Ono Territory from Karyopharm. In the case Ono elects to Manufacture the Licensed Compounds and/or Licensed Products by itself, Ono may Manufacture the Licensed Compounds and/or Licensed Products for Development and Commercialization purposes.

6.2.2 **Commercial Supply Agreement**. If Ono desires to have Karyopharm to supply and Manufacture the Licensed Compounds and/or Licensed Products for the Ono Territory for Commercialization purposes, such Manufacture and supply by Karyopharm shall be covered by a mutually acceptable commercial supply agreement (the "**Commercial Supply Agreement**") which shall include the terms and conditions as are reasonable and customary for an agreement governing the Manufacturing and supply of compounds and/or products similar to the Licensed Compounds and/or the Licensed Products for Commercialization purposes. The purchase price for the Licensed Compounds and/or the Licensed Products shall be [**]. Until the Commercial Supply Agreement is executed,

Karyopharm shall continue to Manufacture and supply the Licensed Compounds and/or the Licensed Products to Ono pursuant to the terms and conditions of the Clinical Supply Agreement, except that the purchase price for the Licensed Compounds and/or the Licensed Products shall be as set forth in this Section 6.2.2.

6.2.3 **Ono's Right to Manufacture**. If Ono elects to Manufacture the Licensed Compounds and/or the Licensed Products by itself in the Field for the Ono Territory for Development and Commercialization purposes, then within [**] after receipt of such request, Karyopharm shall, in accordance with this Section 6.2.3, transfer to Ono, an Affiliate of Ono, or a Third Party manufacturer approved by Karyopharm (such approval not to be unreasonably withheld, delayed or conditioned), the Karyopharm Know-How reasonably necessary or useful to enable Manufacture of the applicable Licensed Compounds and/or Licensed Products for Development and Commercialization for the Ono Territory in the Field and not previously transferred to Ono, such Affiliate of Ono or any such Third Party manufacturer. Such Know-How transfer by Karyopharm shall be conducted using Commercially Reasonable Efforts and shall include copies or samples of relevant documentation, materials, analytical assays for the Licensed Compounds and/or the Licensed Products and other embodiments of such Karyopharm Know-How. Upon such Know-How transfer, Karyopharm shall also make available its qualified technical personnel on a reasonable basis to consult with Ono, such Affiliate of Ono or such Third Party manufacturer with respect to such Karyopharm Know-How. The details of how such Know-How transfer, including a specific list of Karyopharm Know-How to be transferred by Karyopharm, shall be set forth in a written technology transfer plan (the "**Manufacturing Technology Transfer Plan**") executed by the Parties for the purpose of ensuring the complete and timely transfer of such Karyopharm Know-How and the protection of Karyopharm's rights in such Karyopharm Know-How. Manufacturing Technology Transfer Plan shall take into consideration, among other things, the Development and Commercialization activities in the Ono Territory, and the other responsibilities for key employees of Karyopharm. Ono shall pay the amounts set forth in the Manufacturing Technology Transfer Plan for the work and transfer performed by Karyopharm and shall reimburse Karyopharm for its out-of-pocket costs incurred in the course of such transfer pursuant to this Section 6.2.3. Karyopharm shall have no obligation to transfer any Karyopharm Know-How to Ono until the full execution of the Manufacturing Technology Transfer Plan by both Parties. For clarity, during the transfer of such Karyopharm Know-How, Karyopharm shall continue to Manufacture and supply the Licensed Compounds and the Licensed Product to Ono in accordance with Clinical Supply Agreement or Commercial Supply Agreement.

6.3 **Related Substance Supply.** Subject to the terms of the applicable Supply Agreement, Ono shall have the right to purchase from Karyopharm, and Karyopharm shall supply to Ono, related substance of the Licensed Compounds (e.g., reference standard, internal standard and impurities) necessary for Ono to conduct non-clinical studies, preclinical studies or Clinical Studies, including, but not limited to analytical test method development and/or validation, for regulatory submissions or Commercialization in the Ono Territory, at [**].

7. LICENSES

7.1 License Grants.

7.1.1 License Grants to Ono. Subject to the terms and conditions of this Agreement, Karyopharm hereby grants Ono (a) an exclusive (even as to Karyopharm and its Affiliates), royalty-bearing, transferable, sublicenseable (including through multiple tiers) (in accordance with Section 7.2) license under the Karyopharm Technology to Develop, use and Commercialize the Licensed Compounds and the Licensed Products in the Field in the Ono Territory; and (b) subject to election by Ono and the full execution by the Parties of the Manufacturing Technology Transfer Plan, a non-exclusive, royalty-free, non-transferable (except as provided in Section 14.1), sublicenseable (including through multiple tiers) (in accordance with Section 7.2) license under the Karyopharm Technology to Manufacture or have Manufactured Licensed Compounds and Licensed Products in or outside of the Ono Territory solely for Development and Commercialization in the Field in the Ono Territory.

7.1.2 License Grants to Karyopharm. Ono hereby grants Karyopharm a non-transferable (except as provided in Section 14.1), sublicenseable (including through multiple tiers) (subject to Section 7.2), non-exclusive, royalty-free license under Ono Technology to Develop, Manufacture, have Manufactured, use and Commercialize Licensed Compounds and Licensed Products in the Field in the Karyopharm Territory.

7.1.3 License Grants to Karyopharm's Related Party. Karyopharm shall not grant to its Affiliate or any Third Party a license under Karyopharm Technology, which license would materially conflict with Section 7.1.1 (License Grant to Ono). Parties agree that the breach of this provision by Karyopharm shall constitute a "material breach" of this Agreement by Karyopharm.

Karyopharm hereby acknowledges that Ono's rights and status as the exclusive licensee under Karyopharm Technology for the Licensed Products in the Field in the Ono Territory set forth in each of Sections 2.8.2 (Scientific Records), 2.8.4 (Information Sharing), 2.8.5 (Rights of Reference and Access to Data), 3.1.3 and 4.7.1 (Karyopharm Promotional Materials) constitutes essential benefit to enter into this Agreement, provided, however, that, such acknowledgement shall not be made without prejudice to any other benefit conferred to Ono under this Agreement.

Karyopharm shall be responsible for the compliance of its Third Party Licensees with the requirements of Karyopharm's Related Parties in Sections 2.8.2 (Scientific Records), 2.8.4 (Information Sharing), 2.8.5 (Rights of Reference and

Access to Data), 3.1.3 and 4.7.1 (Karyopharm Promotional Materials) (collectively, the "**Collaboration Provisions**"). Karyopharm shall notify Ono in writing whether a Third Party Licensee has agreed to the terms of the Collaboration Provisions promptly after execution of the applicable agreement. If a Third Party Licensee does not agree to any or all of the Collaboration Provisions then Karyopharm shall not grant to such Third Party Licensee the applicable reciprocal rights which may include access to Ono's Data or Ono Technology or which may include (a) the grant of any sublicense under Ono Patent Rights and Ono Know-How to such Third Party Licensee or (b) the grant to such Third Party Licensee of access to Data generated by Ono and Ono Technology or (c) a right of reference with respect to Ono's regulatory filings and Ono's Regulatory Approvals and Ono's promotional materials. For example, if a Third Party Licensee does not agree to grant to Ono the right to cross reference its regulatory filings and Regulatory Approvals related to the Licensed Products, then Karyopharm will not grant to the Third Party Licensee the right to cross reference Ono's regulatory filings and Regulatory Approvals related to the Licensed Products.

If a Third Party Licensee agrees to any or all of the Collaboration Provisions, the applicable reciprocal rights concerning the Licensed Products to be made available by such Third Party Licensee to Ono through Karyopharm shall be incorporated into Karyopharm Technology and shall be granted to Ono under the terms and conditions of this Agreement. Notwithstanding anything herein to the contrary, to the extent that (a) the Party is required by the Regulatory Authority to make available certain Know-How Controlled by Related Party of the other Party (e.g. included, but not limited to, safety information or investigator brochure for Clinical Study conducted by such Related Party) in order to obtain and maintain IND, NDA or Regulatory Approval of Licensed Product or (b) the Party wishes to utilize the Data Controlled by Related Party of the other Party, which is generated from Global Clinical Study, the other Party shall procure and make available to the requesting Party such Know-How and Data, respectively, free of charge.

7.2 Sublicensing Terms.

7.2.1 Ono's Right to Sublicense. Ono may sublicense the rights granted under Section 7.1 to its Related Party with the prior written approval by Karyopharm (such approval not to be unreasonably withheld, delayed or conditioned), provided that Ono is not required for such written approval by Karyopharm and any prior notice to Karyopharm in the cases that:

(a) Ono sublicenses its rights under the Karyopharm Technology to any of its Affiliates;

(b) Ono uses competent and GCP compliant CROs, clinical trial sites or any other Third Party to perform portions of the Development of a Licensed Product to the extent consistent with its normal business practices and Ono Development Plan;

(c) Ono uses Third Party manufacturer to Manufacture Licensed Compound and/or Licensed Product in the Field for the Development and Commercialization for the Ono Territory subject to Section 6.2.3 to the extent that (i) Licensed Compound and/or Licensed Product is Manufactured under direction by Ono and in the manufacturing method approved by Ono and (ii) the specification therefor is approved by Ono; or

(d) Ono engages reasonably qualified Third Parties to assist with Commercialization of the Licensed Products through co-promotion, and distributor arrangements and may sublicense its rights granted under Section 7.1 to such Third Parties to the extent that such arrangements are commercially reasonable and co-promotion and distribution by such Third Parties is made under direction by Ono or strategy given by Ono.

Ono shall promptly provide to Karyopharm written notice of any such grant by Ono in accordance with this Section 7.2.1 except for above (a) through (d) setting forth in reasonable detail the nature of such grant and the identity of the Sublicensee. Any sublicense agreement shall contain confidentiality, reporting, audit and access to data and information obligations comparable to those set forth herein and require the express compliance of such Sublicensee to the requirements set forth in Section 7.1.1(b).

7.2.2 Karyopharm Right to Sublicense. Subject to Section 7.1.3 Karyopharm may sublicense the rights granted under Section 7.1 to its Related Party with the prior written notice to Ono, provided that Karyopharm is not required to make such notice to Ono in the cases that:

(a) Karyopharm sublicenses its rights under the Ono Technology to any of its Affiliates;

(b) Karyopharm uses competent and GCP compliant CROs, clinical trial sites or any other Third Party to perform portions of the Development of a Licensed Product to the extent consistent with its normal business practices;

(c) Karyopharm uses Third Party manufacturer to Manufacture Licensed Compound and/or Licensed Product; or

(d) Karyopharm engages reasonably qualified Third Parties to assist with Commercialization of the Licensed Products through co-promotion, co-marketing and distributor arrangements and may sublicense its rights granted under Section 7.1 to such Third Parties to the extent such arrangements are commercially reasonable.

Karyopharm shall promptly provide to Ono written notice of any such grant by Karyopharm in accordance with this Section 7.2.2 except for above (a) through (d) setting forth in reasonable detail the nature of such grant and the identity of the sublicensee. Any sublicense agreement shall contain confidentiality, reporting, audit and access to data and information obligations comparable to those set forth herein.

7.2.3 Sublicense Requirements. Each sublicense granted by a Party pursuant to Section 7.2 (a "**Sublicense**") to a Third Party shall be in writing

and shall be consistent with the relevant restrictions and limitations set forth in this Agreement. No Sublicense shall diminish, reduce or eliminate any obligation of either Party under this Agreement. Each Party shall remain responsible for its obligations under this Agreement and shall be responsible for the performance of any of its Sublicensees or sublicensees in accordance with applicable terms and conditions of this Agreement.

7.3 Exclusivity.

7.3.1 Karyopharm Exclusivity. During [**], neither Karyopharm nor any of its Affiliates may engage, either alone or in combination with or through any Third Party, in the Development, use and/or Commercialization of (a) any Licensed Compounds and/or Licensed Products in or outside the Field in the Ono Territory; or (b) any compounds and/or products with the Mechanism of Action as a primary mechanism of action in the Field in the Ono Territory.

7.3.2 Ono Exclusivity. During [**], neither Ono nor any of its Affiliates may engage, either alone or in combination with or through any Third Party, in the Development, use and/or Commercializing of any compound or product with the Mechanism of Action as a primary mechanism of action in the Field in the Ono Territory, except that Ono may exercise its rights with respect to the Licensed Compounds and Licensed Products in the Field in the Ono Territory pursuant to this Agreement. If Ono or any of its Affiliates wishes to conduct any such activity, it may provide written notice of such interest to Karyopharm, and Karyopharm may, in its sole discretion, provide its written consent to Ono so that Ono or such Affiliate may conduct such activity.

7.4 No Other Rights. Except as otherwise expressly provided in this Agreement, under no circumstances shall a Party, as a result of this Agreement, obtain any ownership interest, license right or other right in any Know-How, Patent Rights or other intellectual property rights of the other Party, including items owned, controlled or developed by the other Party, or provided by the other Party to the receiving Party at any time pursuant to this Agreement. For clarity, except for Ono's license and rights under Section 7.1,1 relating to Manufacturing of the Licensed Compound and the Licensed Product and other related provisions, (a) in no event will the licenses or rights granted to Ono under this Agreement with respect to the Licensed Compounds and the Licensed Products extend outside the Field and the Ono Territory; (b) Ono's rights with respect to the Licensed Compounds and Licensed Products, and Ono's rights with respect to any regulatory documents and any interactions with Regulatory Authorities with respect to the Licensed Compounds and Licensed Products, shall not extend outside the Field and the Ono Territory; and (c) Ono shall not, directly or indirectly, use, exploit or exercise any rights under any Karyopharm Technology, or otherwise conduct any Development, use, or Commercialization activities with respect to any Licensed Compound or Licensed Product, outside the Field or outside the Ono Territory. In addition, for clarity, (a) in no event will the licenses or rights granted to Karyopharm under this Agreement with respect to the Licensed Compounds and the Licensed Products extend outside the Field and the Karyopharm Territory; (b) Karyopharm's rights under the Ono Technology with respect to the Licensed Compounds and Licensed Products, and

Karyopharm's rights with respect to any regulatory documents and any interactions with Regulatory Authorities with respect to the Licensed Compounds and Licensed Products, shall not extend outside the Karyopharm Territory; and (c) Karyopharm shall not, directly or indirectly use, exploit or exercise any rights under any Ono Technology, or otherwise conduct any Development, use, Manufacturing, having Manufactured or Commercialization activities with respect to any Licensed Compound or Licensed Product outside the Field and outside the Karyopharm Territory.

8. CERTAIN FINANCIAL TERMS

8.1 Upfront Fee. In consideration for the rights, licenses and options granted by Karyopharm to Ono under this Agreement, Ono shall pay Karyopharm a non-refundable, non-creditable upfront payment of Two and a Half Billion Japanese Yen (JPY2,500,000,000), within [**] of receipt by Ono of invoice for such upfront fee and the taxation documents expressly described in Section 8.11.

8.2 Development Milestone Payments.

8.2.1 Ono shall make the non-refundable, non-creditable milestone payments to Karyopharm set forth below in this Section 8.2.1 (the "**Development Milestone Payment(s)**"), each payable once, within [**] of receipt by Ono of an invoice for corresponding Development Milestone Payment and taxation documents expressly described in Section 8.11.

Development Milestone Event – Multiple Myeloma	Development Milestone Payment (in JPY)	
	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]

Development Milestone Event – Additional Indications*	Development Milestone Payment (in JPY)
[**]	[**]
[**]	[**]
[**]	[**]
Development Milestone Event – ASEAN and Hong Kong countries	
[**]	[**]

The total amount of the Development Milestone Payments to be paid by Ono to Karyopharm shall not exceed Ten Billion and One Hundred Fifty Million Japanese Yen (¥10,150,000,000).

* Each Development Milestone Payment for the Indications as set forth in this section 8.2.1 shall be made only once with respect to the achievement of each milestone event (the "**Development Milestone Event**") above, regardless of subsequent or repeated achievement of such Development Milestone Event by any Licensed Compound or Licensed Product. [**].

8.2.2 Each Development Milestone Payment by Ono to Karyopharm hereunder shall be payable only once, regardless of the number of times achieved with respect to a Licensed Product.

8.2.3 Ono shall provide Karyopharm with written notice of the achievement by Ono or any of its Related Parties of any Development Milestone Event with respect to a Licensed Product set forth in Section 8.2.1 within [**] after the occurrence of such Development Milestone Event; provided, however, that Ono shall inform Karyopharm of such Development Milestone Event prior to any public disclosure of such Development Milestone Event by Ono.

8.3 Sales Milestone Payments.

8.3.1 Ono shall provide Karyopharm with written notice of the achievement by Ono or any of its Related Parties of any milestone event with respect to a Licensed Product set forth in this Section 8.3.1 (the "**Sales Milestone Event**") within [**] after the occurrence of each Sales Milestone Event. Ono shall make the non-refundable, non-creditable payments to Karyopharm set forth below in this Section 8.3.1 (the "**Sales Milestone Payment(s)**") within [**] of receipt by Ono of an invoice for corresponding Sales Milestone Payment and taxation documents expressly described in Section 8.11:

Sales Milestone Event	**Sales Milestone Payment (in JPY)**
(i) First achievement of Annual Net Sales of the Licensed Products in the Ono Fiscal Year greater than [**]	[**]
(ii) First achievement of Annual Net Sales of the Licensed Products in the Ono Fiscal Year greater than [**]	[**]
(iii) First achievement of Annual Net Sales of the Licensed Products in the Ono Fiscal Year greater than [**]	[**]

The total amount of the Sales Milestone Payments to be paid by Ono to Karyopharm shall not exceed Nine Billion Japanese Yen (¥9,000,000,000).

8.3.2 Sections 8.2.2 shall apply for the Sales Milestone Payment. If a Sales Milestone Event described in a clause in Section 8.3.1 occurs before or concurrently with another Sales Milestone Event described in a preceding clause in Section 8.3.1, Ono shall also pay the Sales Milestone Payment described in such earlier clause when the Sales Milestone Payment described in such later clause is paid. By way of example, if, during an Ono Fiscal Year, Annual Net Sales of Licensed Products first exceed the thresholds set forth in Sections 8.3.1(i) and (ii), Ono shall pay Karyopharm the Sales Milestone Payments set forth in both Sections 8.3.1(i) and (ii).

8.4 Royalties.

8.4.1 Royalties Payable on Licensed Products. Subject to Sections 1.50, 1.80, 8.4.1, 8.4.2 and 8.4.3, during the Royalty Term, Ono shall pay to Karyopharm a royalty of (a) [**] percent ([**]%) on Net Sales of a Licensed Product by Ono and its Related Parties of all Licensed Products in the Ono Territory. For purpose of this Agreement, the "**Royalty Term**" means the period which commences upon the date of First Commercial Sale and continues until the later of (a) the date of expiration of the first Regulatory Exclusivity period applicable to the Licensed Product in such country in the Ono Territory (which shall not be extended by grant of the second Regulatory Exclusivity Period); (b) the date of expiration of all Karyopharm Patent Rights, whose Valid Claim Covers such Licensed Product, or (c) the tenth (10th) anniversary of the First Commercial Sale of such Licensed Product in the Field (which shall not be extended by launch of any other formulation or dosage form of the same API as in such Licensed Product). Such Royalty Term shall be established on Licensed Product-by-Licensed Product and country-by-country basis.

8.4.2 **Royalty Reduction by Entry of Generic Version** If at any time during the period from the date of First Commercial Sale of a Licensed Product until the tenth (10th) anniversary of such First Commercial Sale of such Licensed Product, any Third Party (other than a Sublicensee) makes a Generic Version (defined below) of such Licensed Product commercially available in such country in the Ono Territory, then the royalty rate applicable to Net Sales of such Licensed Product in such country shall be reduced to [**] percent ([**]%). If (a) at any time following the tenth (10th) anniversary of the First Commercial Sale of a Licensed Product, any Third Party (other than a Sublicensee) makes a Generic Version of such Licensed Product commercially available in such country in the Ono Territory or (b) prior to the tenth (10th) anniversary of the First Commercial Sale of a Licensed Product, any Third Party (other than a Sublicensee) makes a Generic Version of such Licensed Product commercially available in such country in the Ono Territory and such Generic Version is marketed as of such tenth (10th) anniversary, then [**] shall be payable on the Net Sales of such Licensed Product in such country during the remainder of the Royalty Term. "**Generic Version**" means a product that: (a) contains as an active pharmaceutical ingredient a chemical composition that is assigned the same INN (international nonproprietary name) or JAN (Japanese Accepted Names for Pharmaceuticals) as is assigned to active pharmaceutical ingredient contained in the corresponding Licensed Product being marketed in the Ono Territory; (b) obtained marketing approval in a country in the Ono Territory by means of an abridged procedure that relies (i) in whole or in part on the safety and efficacy data contained in the NDA for such Licensed Product submitted by Ono in such country, and (ii) on establishing bioequivalence to the Licensed Product; and (c) is legally marketed in the Ono Territory by an entity other than Ono, its Affiliates or its Sublicensees without infringing any Valid Claim of Karyopharm Patent Rights.

8.4.3 **Stacking.** The applicable royalty due pursuant to Section 8.4.1 shall be adjusted as follows: If Ono or any of its Affiliates determines in good faith that, in order to avoid infringement of any Third Party's Patent Right, it is reasonably necessary to obtain a license after the Effective Date from a Third Party under one or more Valid Claims owned or licensable by such Third Party Covering the composition of matter, method of making (including method of formulation if no other comparable method of formulation is available without requiring Ono or its Related Party to obtain a license) or method of use of a Licensed Product in order for Ono and its Related Parties to Manufacture or have Manufactured in the Field for a country in the Ono Territory such Licensed Product, or Develop, use or Commercialize in the Field in a country in the Ono Territory such Licensed Product and to make payments under such license, and Ono or any Related Party actually enters into any such license, then the amount of Ono's royalty payments under Section 8.4.1 for such Licensed Product in such country in a Calendar Quarter may be reduced by [**] percent ([**]%) of the

royalties actually paid by Ono or any of its Affiliates to such Third Party to the extent applicable to such Licensed Product in such country during such Calendar Quarter; provided, however, that in no event shall the amounts paid to Karyopharm be reduced below [**] percent ([**]%) of the amounts that would otherwise have been payable, as determined pursuant to Section 8.4.1, and Ono may carry such royalty amounts which should be reduced in accordance with Section 8.4.2 and 8.4.3 forward for reduction against milestone payments and royalties payable with respect to Net Sales of such Licensed Product in such country in future Calendar Quarters until fully applied.

8.4.4 Limits on Deductions. In no event shall the cumulative effect of the adjustments in Section 8.4.3 reduce the royalties payable to Karyopharm pursuant to Section 8.4.1 to less than [**] percent ([**]%) of the amounts that would otherwise have been payable, as determined pursuant to Section 8.4.

8.5 Reports; Payment of Royalty. During the Term, following the First Commercial Sale of the Licensed Product in any country in the Ono Territory, Ono shall furnish to Karyopharm (a) an estimate within [**] after the end of each Calendar Quarter of the Net Sales of each Licensed Product in each country of the Ono Territory and the royalties payable under this Agreement; and (b) a written report (each, a "**Royalty Report**") within [**] after the end of each Calendar Quarter showing, on a Licensed Product-by-Licensed Product and country-by-country basis, the Net Sales of each Licensed Product in each country of the Ono Territory and the royalties payable under this Agreement, along with (i) gross sales of the Licensed Product in the Ono Territory in the relevant Calendar Quarter on a country-by-country basis, (ii) Net Sales in the relevant Calendar Quarter on a country-by-country basis, (iii) all relevant exchange rate conversions in accordance with Section 8.8.3, (iv) all deductions in accordance with Sections 1.57 and 8.4 and (v) the amount of any payment due from Ono to Karyopharm, calculated in accordance with this Article 8. Simultaneously with the delivery of each such Royalty Report, Ono shall pay to Karyopharm the total amounts due under Section 8.4 for the period covered by such Royalty Report subject to Ono's receipt of taxation documents expressly described in Section 8.11. Ono and its Related Parties involved in Commercializing Licensed Products shall keep complete and accurate records in sufficient detail to enable the royalties and other payments payable hereunder to be determined. In addition, Ono and its Related Parties shall comply with any applicable reporting requirements under the Karyopharm Third Party Agreements.

8.6 Audits.

8.6.1 Ono shall keep, and shall require its Related Parties to keep, full, true and accurate books of account containing all particulars that may be necessary for the purpose of calculating the amounts payable by Ono under this Agreement, including, as applicable, records of Development activities and Net Sales, and the amount of Joint Patent Costs payable by Karyopharm with respect to Joint Patent Rights pursuant to Section 12.4.3. Karyopharm shall keep, and shall require its Related Parties to keep, full, true and accurate books of account containing all particulars that may be necessary for the purpose of calculating the amounts payable by Ono under this Agreement, including, as applicable, records

of Manufacturing activities and Karyopharm's Cost of Manufacturing for the Licensed Compound and Licensed Product, and Joint Patent Costs payable by Ono with respect to Joint Patent Rights pursuant to Section 12.4.3. Such books of accounts shall be kept at each Party's principal place of business for a period of at least [**] Calendar Years after the date on which the relevant Development or Manufacturing activity or Net Sales occurred or the relevant Joint Patent Costs were incurred. Either Party (the "**Auditing Party**") has the right, at its expense (except as set forth below), to engage an independent, certified public accountant selected by such Auditing Party and reasonably acceptable to the other Party (the "**Auditor**") to perform, on behalf of such Auditing Party, an audit of such books and records that are deemed necessary by such Auditor to report on the correctness of any report or payments made or to have been made under this Agreement.

8.6.2 The Auditing Party shall provide reasonable, but at least [**], prior written notice to the other Party of any requested audit and shall conduct such audit during regular business hours in such a manner as to not unnecessarily interfere with the other Party's normal business activities. Any audit shall be limited to records for the [**] Calendar Years prior to audit notification. The Auditing Party shall not perform an audit more frequently than [**] nor more frequently than [**] with respect to records covering any specific period of time, except if Karyopharm is required to do so pursuant to a Karyopharm Third Party Agreement.

8.6.3 The Auditing Party shall use all such records of the other Party only for the purpose of verifying payments due hereunder, and shall treat such records as the other Party's Confidential Information. The Auditor shall be obligated to execute a reasonable confidentiality agreement with the other Party prior to commencing any such audit. The Auditor shall only share the results of the audit, not the underlying records, with the Auditing Party. Any final audit report shall be shared by the Auditing Party with the other Party.

8.6.4 Notwithstanding Section 8.6.1, if the audit uncovers an underpayment in any Calendar Quarter by a Party, or an overpayment in any Calendar Quarter by a Party, that exceeds [**] percent ([**]%) of the total payment owed, then the reasonable out-of-pocket fees incurred by the Auditing Party with respect to such audit shall be paid by the other Party. In the event such audit leads to the discovery of a discrepancy to the Auditing Party's detriment, the other Party will pay any undisputed underpaid amount of the discrepancy, plus interest on the underpayment at a rate per annum equal set forth in Section 8.9 within [**] after receipt by the other Party of an invoice for corresponding payment and taxation documents delivered from the Auditing Party, subject to the other Party's receipt of such final audit report from the Auditor.

8.7 **Karyopharm Third Party Agreement Payments**. Karyopharm shall be solely responsible for any royalties or other payments due under the Karyopharm Third Party Agreements.

8.8 Exchange Rate.

8.8.1 Payment Method. All payments to be made by Ono under this Agreement shall be made by bank wire transfer in immediately available funds to bank account as may be designated by Karyopharm from time to time. The first designated bank account of Karyopharm shall be as follows:

Account name:	[**]
Account number:	[**]
Bank name:	[**]
Beneficiary Address:	[**]
Swift code:	[**]
Routing/Transit for Wires:	[**]
Routing/Transit for ACH	[**]

8.8.2 Currency Conversion. All amounts specified in this Agreement are in Japanese Yen. All payments hereunder shall be made in US Dollars. In the case Ono makes payment under this Agreement, all such payment shall be converted into US Dollars at the exchange rate (TTS rate) for the conversion of Japanese Yen into US Dollars posted by the Bank of Tokyo-Mitsubishi UFJ, Ltd., on the date on which Ono will make the applicable payment hereunder, provided that no deduction from any amount shall be made in respect of bank fees or charges.

8.8.3 Conversion of Net Sales. In the case of Net Sales made in one or more currencies other than Japanese Yen during a Calendar Quarter (each a "**Third-Country Currency**"), Net Sales will be converted from each relevant Third-Country Currency to such Third-Country Currency's equivalent in Japanese Yen. The amount of Net Sales made during any Calendar Quarter shall be determined by converting the portion of such Net Sales made in each Third-Country Currency into Japanese Yen, using the exchange rate for the conversion of foreign currency into Japanese Yen posted by the Bank of Tokyo-Mitsubishi UFJ, Ltd., between the relevant Third-Country Currency, on the one hand, and Japanese Yen, on the other hand. All currency conversions described in this Section 8.8.3 shall be made in accordance with IFRS, to the extent reasonable and consistently applied.

8.9 Late Payments. Any amount owed by a Party to the other Party under this Agreement that is not paid on or before the date such payment is due shall bear interest at a rate per annum equal to [**] percent ([**]%) per month, calculated based on the number of days such payments are paid after the date such payments are due, compounded monthly and computed on the basis of a year of three hundred sixty-five (365) days for the actual number of days' payment is delinquent.

8.10 Blocked Payments. If, by reason of Law in any jurisdiction in the Ono Territory, it becomes impossible or illegal for Ono to transfer milestone payments, royalties or other payments under this Agreement to Karyopharm, (a) Ono shall promptly notify Karyopharm; and

(b) Ono shall pay Karyopharm the amounts due from an account in another jurisdiction in the Ono Territory; provided, however, that if there is no jurisdiction in the Ono Territory from which it is legal for Ono to transfer payments to Karyopharm (i) Ono shall deposit such payments in local currency in the relevant jurisdiction to the credit of Karyopharm in a recognized banking institution designated by Karyopharm or, if none is designated by Karyopharm within a period of [**], in a recognized banking institution selected by Ono and identified in a written notice given to Karyopharm, and (ii) Karyopharm may terminate this Agreement if Ono is not permitted by Law to transfer payments to Karyopharm for a period of [**].

8.11 Taxes. In the event that Ono is required to withhold and pay over any tax to the Governmental Authorities in any country in the Ono Territory in respect of any payment to Karyopharm, the amount thereof shall be deducted from the payment to be made by Ono and timely and properly paid over to such Governmental Authorities, provided that Ono shall furnish Karyopharm with copies of receipts and other documentation evidencing such withholding. Karyopharm shall provide to Ono any taxation documents (Form 3 and Form 17), and the Residency Certificate (Form 6166) of Karyopharm issued by the US Internal Revenue Service (which Residency Certificate is effective for three (3) years after its issuance to a public company) and other documents that may be reasonably necessary in order for Ono not to withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Without limiting the foregoing, the Parties shall exercise their reasonable efforts to ensure that any withholding taxes imposed are reduced as far as possible under the provisions of any applicable tax treaty, and shall cooperate in filing any forms required for such reduction. Each Party shall cooperate with the other and furnish the other Party with appropriate documents to secure application of the most favorable rate of withholding tax under applicable Law (or exemption from such withholding tax payments, as applicable).

9. CONFIDENTIALITY AND PUBLICATION

9.1 Nondisclosure Obligation.

9.1.1 Except with the prior written consent of the Disclosing Party or as otherwise set forth herein, during the Term and for a period of [**] after any termination or expiration of this Agreement, all Confidential Information of the Disclosing Party (a) shall be maintained in confidence by the Receiving Party, (b) shall not be disclosed by the Receiving Party to an Affiliate or Third Party, and (c) shall not be used by the Receiving Party for any purpose except to perform its obligations and to exploit its rights under this Agreement.

9.1.2 Notwithstanding the obligations of confidentiality and non-use set forth above, subject to Section 7.1.3, the Receiving Party may provide the Disclosing Party's Confidential Information, and disclose the existence and terms of this Agreement, as may be reasonably required in order to perform its obligations and to exploit its rights under this Agreement, and specifically (a) to its Related Parties, and the Receiving Party's and its Related Parties' employees, directors, officers, agents, consultants, advisors or other Third Parties who need to

know the Confidential Information of the Disclosing Party for the performance of its obligations or to exercises its rights hereunder (or for such Persons to determine their interest in performing such activities) in accordance with this Agreement, in each case who are under an obligation of confidentiality with respect to such Confidential Information that is no less stringent than the terms of this Section 9.1, provided that, it being understood that, notwithstanding any other provision of this Agreement, in the case of disclosures made to clinical trial sites, investigators, CROs or other Third Parties involved in the Development of the Licensed Compound or Licensed Product, the duration for the obligation of confidentiality and non-use provided in a Party's agreement with such clinical trial sites, investigators, CROs or other Third Parties may be less than the duration for the obligation of confidentiality and non-use in this Agreement so long as such agreement specifies a duration for the obligation of confidentiality and non-use at least [**] from the expiration or termination date of such agreement with clinical trial sites, investigators, CROs or other Third Parties; (b) to Governmental Authorities or Regulatory Authorities in order to seek or obtain Patent Rights or Regulatory Approvals in a manner not inconsistent with this Agreement or to perform its obligations or exploit its rights under this Agreement; provided that such Confidential Information shall be disclosed only to the extent reasonably necessary to do so; (c) to the extent required by Governmental Authority or Law; and (d) to its actual or bona fide prospective acquirers, underwriters, investors, lenders or other financing sources, its actual or bona fide prospective collaborators, licensors, licensees or strategic partners, and to its consultants and advisors with respect to any actual or bona fide prospective acquisition, sale, financing or collaboration of the Receiving Party, in each case who are under an obligation of confidentiality with respect to such information that is no less stringent than the terms of this Section 9.1, provided that such Confidential Information is disclosed only to the extent reasonably necessary to do so. In addition, Karyopharm may disclose Ono's Confidential Information to the counterparty to any Karyopharm Third Party Agreement, which is under an obligation of confidentiality with respect to such Confidential Information that is no less stringent than the terms of this Section 9.1, to comply with such Third Party Agreement, provided that such Confidential Information is disclosed only to the extent reasonably necessary to do so and Karyopharm shall be fully responsible for compliance with such an obligation of confidentiality and non-use by such counterparty to any Karyopharm Third Party Agreement. If the Receiving Party is required by Governmental Authority or Law to disclose the Disclosing Party's Confidential Information, the Receiving Party shall, to the extent consistent with Law, promptly inform the Disclosing Party of the required disclosure in order to provide the Disclosing Party an opportunity to challenge or limit the disclosure obligations. Confidential Information that is required to be disclosed by Governmental Authority or Law shall remain otherwise subject to the confidentiality and non-use provisions of this Section 9.1. If a Party concludes that a copy of this Agreement shall be filed with the U.S. Securities and Exchange Commission or similar regulatory agency in a country other than the United States, then, to the extent consistent with Law, such Party will provide the other

Party with a copy of this Agreement showing any provisions hereof as to which the Party proposes to request confidential treatment, will provide the other Party with an opportunity to comment on any such proposed redactions and to suggest additional redactions, and will take such Party's reasonable and timely comments into consideration before filing this Agreement.

9.2 Publication and Publicity.

9.2.1 Publication. Ono and Karyopharm each acknowledge the other Party's interest in publishing certain key results of the activities conducted under this Agreement. Ono may publish or publicly disclose such results with respect to a Clinical Study or Development activity that is part of Ono's Development Plan in which Karyopharm is not participating, subject to Karyopharm's right to review as required in this Section 9.2.1. Karyopharm may publish or publicly disclose results from any of its activities, subject to Ono's right to review as required in this Section 9.2.1. Each Party also recognizes the mutual interest in obtaining valid patent protection and in protecting trade secret information. Consequently, except for disclosures permitted pursuant to Section 9.1 and 9.2.2(a) through (c), in case Ono wishes to make a publication or public presentation that pertains to results concerning Licensed Compound(s) or Licensed Product(s) which has not been previously disclosed, Ono shall deliver to the other Party a copy of the proposed written publication or presentation at least [**] prior to submission for publication or presentation. Except for disclosures permitted pursuant to Section 9.1 and 9.2.2(a) through (c), in case that Karyopharm wishes to make (i) a publication or public presentation that pertains to results concerning Licensed Compound(s) or Licensed Product(s) in an internationally recognized publication or conference or (ii) a publication or public presentation that, Karyopharm reasonably judges, contains Confidential Information of Ono, Karyopharm shall deliver to Ono a copy of the proposed written publication or presentation at least [**] prior to submission for publication or presentation. The reviewing Party shall have the right (a) to propose modifications to the publication or presentation for patent reasons, trade secret reasons or business reasons, and the publishing Party will remove all Confidential Information of the reviewing Party if requested by the reviewing Party, and (b) to request a reasonable delay in publication or presentation in order to protect patentable information. If the reviewing Party requests a delay, the publishing Party shall delay submission or presentation for a period of [**] (or such shorter period as may be mutually agreed by the Parties considering the time constraints for submission to a particular conference or journal) to enable the non-publishing Party to file patent applications protecting such Party's rights in such information in accordance with Article 12 or may agree to remove the patentable information from the publication or presentation in question. With respect to any proposed publications or disclosures by investigators or academic or non-profit collaborators working with a Party, such materials shall be subject to review and delay under this Section 9.2 to the extent that such Party has the right and ability (after using Commercially Reasonable Efforts to obtain such right and ability) to do so.

9.2.2 Publicity. Except as set forth in Section 9.1 above and Section 9.2.2(a) through (c) below, the terms of this Agreement may not be disclosed by either Party, and no Party shall use the name, trademark, trade name or logo of the other Party

or its employees in any publicity, news release or disclosure relating to this Agreement, its subject matter or the activities of the Parties hereunder without the prior express written permission of the other Party, except as may be required by Law or expressly permitted by the terms hereof.

(a) Following the execution of this Agreement, the Parties shall issue a joint press release of which content shall be mutually agreed between the Parties. After such initial press release, except as provided in Section 9.2.2(b), neither Party shall issue a press release or public statement relating to this Agreement without the prior written approval of the other Party, which approval shall not be unreasonably withheld, conditioned or delayed, except that a Party may (i) once a press release or other public statement has been made by a Party in accordance with this Agreement, make subsequent public disclosure of any of the information contained in such press release or other written statement, without the approval of the other Party, and (ii) upon prior written notice, to the extent permitted under applicable Law, to the other Party, issue a press release or public announcement as required, in the reasonable judgment of such Party, by Law.

(b) In addition, either Party may, upon prior written notice, to the extent permitted under applicable Law, to the other Party, issue a press release or make a public disclosure relating to such Party's Development, use, Manufacturing, having Manufactured or Commercialization activities with respect to Licensed Products in the Field in accordance with this Agreement and Karyopharm may, upon a prior written notice to Ono, issue a press release or make a public disclosure relating to the Development, use, Manufacturing, having Manufactured or Commercialization activities with respect to Licensed Products outside the Field, provided that such press release or public disclosure does not disclose Confidential Information of the other Party. The Party wishing to issue such press release or make such a public disclosure shall provide the other Party with such draft at least [**] prior to such press release or public disclosure for other Party's review. The reviewing Party shall have the right to propose modifications to such press release or public disclosure for patent reasons or, trade secret reasons or business reasons, and the publishing Party will remove all Confidential Information of the reviewing Party if requested by the reviewing Party. Notwithstanding the foregoing, a Party may issue such press release or make such a public disclosure without [**] prior written notice to the other Party if in the reasonable judgment of such Party, such press release or public disclosure within the period shorter than [**] is required by Law, provided that the Party shall provide the other Party with a copy of such press release or other public disclosure no later than when it is issued or released. Either Party may publicly announce or disclose without regard to the preceding requirements of this Section 9.2.2(b) any information that was previously publicly disclosed pursuant to this Section 9.2.2(b). Furthermore, either Party may issue a full translation of a press release or public disclosure to be issued by the other Party.

(c) Each Party shall be entitled to include the name and picture of the other Party within a list of collaborators with consent of the other Party. Once a Party obtains such consent from the other Party, such Party may use the name and picture of such other Party in a Party's annual report, company brochure or website and so on, and such Party may continue to use them in the same.

10. REPRESENTATIONS, WARRANTIES AND COVENANTS; DISCLAIMER

10.1 **Mutual Representations and Warranties.** Each Party represents and warrants to the other Party that as of the Effective Date:

10.1.1 It is duly organized and validly existing under the Law of its jurisdiction of incorporation or formation, and has full corporate or other power and authority to enter into this Agreement, and to carry out the provisions hereof;

10.1.2 It is duly authorized to execute and deliver this Agreement, and to perform its obligations hereunder, and the individual(s) executing this Agreement on its behalf has been duly authorized to do so by all requisite corporate action;

10.1.3 This Agreement is legally binding upon it and enforceable in accordance with its terms, subject to the general principles of equity and to bankruptcy, insolvency, moratorium and other similar Law affecting the enforcement of creditors' rights generally;

10.1.4 The execution, delivery and performance of this Agreement by it does not conflict with any agreement, instrument or understanding, oral or written, to which it is a party and by which it may be bound, or with its charter or by-laws;

10.1.5 Neither the execution and delivery of this Agreement nor the performance hereof by such Party requires such Party to obtain any permit, authorization or consent from any Governmental Authority (except for any intellectual property rights, INDs, Regulatory Approvals, pricing or reimbursement approvals, Manufacturing-related approvals or similar approvals necessary for Manufacture or having Manufactured in the Field for the Ono Territory, or Development, use or Commercialization in the Field in the Ono Territory, of the Licensed Product as set forth herein), or, to its and its Affiliates' Knowledge, from any other Person;

10.1.6 It has not granted any right to any Third Party that would conflict with the rights granted to the other Party hereunder; and

10.1.7 Neither it nor any of its Affiliates has been debarred or is subject to debarment and neither Party nor any of its Affiliates has, to its Knowledge, used in any capacity, in connection with its Development of the Licensed Compound or the Licensed Product, any Person that has been debarred pursuant to Section 306 of the U.S. Federal Food, Drug, and Cosmetic Act, as amended, or any comparable Law in any country, or that is the subject of a conviction described in such section or any comparable Law in any country.

10.2 **Representations and Warranties of Karyopharm.** Karyopharm represents and warrants to Ono that as of the Effective Date:

10.2.1 Karyopharm is the sole and exclusive owner of, or otherwise Controls, the Karyopharm Technology and has the right to grant the licenses to the Karyopharm Technology to Ono pursuant to this Agreement;

10.2.2 To the Knowledge of Karyopharm and its Affiliates, Schedule 10.2.2 is an accurate listing of all Karyopharm Patent Rights owned or Controlled by Karyopharm or its Affiliates as of the Effective Date that are necessary or useful for Manufacture or having Manufactured in the Field for the Ono Territory, or Development, use or Commercialization in the Field in the Ono Territory, of the Licensed Product;

10.2.3 Any Karyopharm Technology is free and clear of liens, charges or encumbrances;

10.2.4 To the Knowledge of Karyopharm and its Affiliates, any Karyopharm Patent Rights specified in Schedule 10.2.2 are not invalid or unenforceable in whole or part or, as to patent application, has not lapsed, or in the case of a provisional patent application has not been cancelled, withdrawn or abandoned without the possibility of revival;

10.2.5 To the Knowledge of Karyopharm and its Affiliates, except manufacture and supply of Licensed Compound as reagent by reagent supplier, there is no material infringement or misappropriation of any Karyopharm Technology by any Third Party;

10.2.6 To the Knowledge of Karyopharm and its Affiliates, any Person who was involved in the invention for the Karyopharm Patent Rights, has executed and delivered to Karyopharm or its Affiliates, as the case may be, an agreement assigning to Karyopharm (or its applicable Affiliate) all rights, titles and interests in and to all the inventions for the Karyopharm Patent Rights arising out of or relating to such Person's activities with respect to the Licensed Compound and the Licensed Product;

10.2.7 Karyopharm and its Affiliates have generated, prepared, maintained and retained all Data and regulatory documentation that is required to be generated, maintained or retained pursuant to and in accordance with GLP and GCP and applicable Law in all material respects, and all such Data and regulatory documentation are true, complete and correct and what it purports to be. Karyopharm and its Affiliates have conducted, (and each of their respective contractors and consultants have conducted) its research and Development activities in accordance with applicable GLP and GCP and applicable Law in each case in all material respects, provided, however, with respect to any information provided by Karyopharm to Ono prior to the Effective Date relating to any Relevant Clinical Studies, Ono acknowledges and agrees that such information is preliminary, based on unaudited clinical site data and will not be finalized until the completion of data analysis, lock and transfer;

10.2.8 Karyopharm has disclosed or made available to Ono all material information in its or its Affiliates' possession and Control relating to the Licensed Compound and the Licensed Product, and the Development, Manufacture, use and Commercialization of the Licensed Compound and the Licensed Product as conducted prior to the Effective Date, including by providing or making available complete and correct copies of the following: (a) adverse event reports; (b) clinical study reports and material study data; and (c) FDA inspection reports, notices of adverse findings, warning letters, Regulatory Approval filings and other material regulatory documentation;

10.2.9 To the Knowledge of Karyopharm and its Affiliates, there are no, and there have been no, material safety issues relating to the Licensed Compound or the Licensed Product;

10.2.10 Except as has been disclosed to Ono by Karyopharm, Karyopharm and its Affiliates are not aware of any fact or circumstance that would reasonably be expected to materially adversely affect the acceptance or the subsequent approval, by Regulatory Authority of any filing, application or request for Regulatory Approval;

10.2.11 Karyopharm and its Affiliates are not aware of, and has not received, any written notice of (a) any actual or threatened claim that any issued patent or trade secret right owned or controlled by a Third Party would be infringed or misappropriated by the Development, Manufacture, use or Commercialization of the Licensed Products in the Field in the Ono Territory and Karyopharm Territory, or (b) any threatened claims or litigation seeking to invalidate or otherwise challenge the Karyopharm Patent Rights or Karyopharm's or its Affiliates' rights therein;

10.2.12 Karyopharm and its Affiliates have taken commercially reasonable steps to protect, preserve and maintain the confidentiality of all confidential or non-public information included in Karyopharm Know-How, including by disclosing such Karyopharm Know-How to Third Parties only under terms of confidentiality. To the Knowledge of Karyopharm and its Affiliates, no breach of such confidentiality obligations has been committed by any Third Party;

10.2.13 To the Knowledge of Karyopharm and its Affiliates, neither Karyopharm nor its Affiliates, nor any of its or their respective directors, officers, employees or agents has (a) committed an act, (b) made a statement or (c) failed to act or make statement, in any case ((a), (b) or (c)), that (x) would be or create an untrue statement of material fact or fraudulent statement to the FDA or any other Regulatory Authority with respect to the Development, Manufacture, having Manufactured, use or Commercialization of the Licensed Compound or the Licensed Product or (y) could reasonably be expected to provide a basis for the FDA or any other Regulatory Authority to invoke its policy respecting "Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities", set forth in

56 Fed. Reg. 46191 (September 10, 1991) and any amendments thereto or any analogous laws or policies, with respect to the Development, Manufacture, having Manufactured, use or Commercialization of the Licensed Compound or the Licensed Product; and

10.2.14 With respect to each Karyopharm Third Party Agreement set forth on Schedule 1.43, (a) Karyopharm is not in breach under such Third Party Agreement; (b) Karyopharm has not received any notice of breach under such Third Party Agreement; and (c) Karyopharm has previously provided Ono with access to true and complete copies of such Third Party Agreement; provided, however, that Confidential Information of Karyopharm or confidential information of its counterparty may have been redacted from such copies.

10.3 Mutual Covenants. During the Term, each Party covenants as follows;

10.3.1 It will not enter into any agreement, instrument or understanding, oral or written, with any Third Party which conflicts with this Agreement;

10.3.2 It will not grant any right to any Third Party that would conflict with the rights granted to the other Party hereunder; and

10.3.3 It will not, and it will use Commercially Reasonable Efforts to ensure its Related Parties will not conduct any activities which would be subject to debarment and neither Party will use in any capacity, and either Party will use Commercially Reasonable Efforts to ensure any Related Party will not use, in connection with the performance of its obligations under this Agreement, any Person that has been debarred pursuant to Section 306 of the U.S. Federal Food, Drug, and Cosmetic Act, as amended, or any comparable Law in any country, or that is the subject of a conviction described in such section or any comparable Law in any country. Each Party agrees to inform the other Party in writing immediately if it or any Person that is performing activities under this Agreement, is debarred or is subject to debarment or is the subject of a conviction described in such Section 306, or any comparable Law in any country, or if any action, suit, claim, investigation or legal or administrative proceeding is pending or, to the notifying Party's Knowledge, is threatened, relating to the debarment or conviction of the notifying Party or any Person used in any capacity by such Party or any of its Related Party in connection with the performance of its obligations under this Agreement.

10.4 Karyopharm's Covenants. During the Term, Karyopharm covenants as follows;

10.4.1 Any Karyopharm Technology will be free and clear of liens, charges or encumbrances except for any liens, charges or encumbrances that may be incurred in connection with a financing arrangement by Karyopharm, provided that such liens, charges or encumbrances will not affect the ability of Ono to Develop, use, obtain Regulatory Approval for and Commercialize the Licensed Products in the Field in each country in the Ono Territory and to Manufacture the Licensed Compound and Licensed Product in the Field for the Ono Territory; and

10.4.2 With respect to each Karyopharm Third Party Agreement set forth on Schedule 1.43, Karyopharm will not conduct any activities that would be reasonably expected to result in a breach of any such Third Party Agreement which would affect the license grant to Ono under this Agreement; and

10.4.3 Karyopharm will obtain Katholieke Universiteit Leuven's assurances that it will not act adversely to affect the license grant to Ono under this Agreement.

10.5 Warranty Disclaimer. EXCEPT AS OTHERWISE EXPRESSLY PROVIDED IN THIS AGREEMENT, NEITHER PARTY MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, TO THE OTHER PARTY WITH RESPECT TO ANY TECHNOLOGY, LICENSED COMPOUND, LICENSED PRODUCT, GOODS, SERVICES, RIGHTS OR SUBJECT MATTER OF THIS AGREEMENT AND EACH PARTY HEREBY DISCLAIMS ALL IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE AND NON-INFRINGEMENT WITH RESPECT TO ANY AND ALL OF THE FOREGOING. EACH PARTY HEREBY DISCLAIMS ANY REPRESENTATION OR WARRANTY THAT THE DEVELOPMENT, USE, MANUFACTURE, HAVING MANUFACTURED OR COMMERCIALIZATION OF THE LICENSED COMPOUNDS OR THE LICENSED PRODUCTS PURSUANT TO THIS AGREEMENT WILL BE SUCCESSFUL OR THAT ANY PARTICULAR SALES LEVEL WITH RESPECT TO A LICENSED PRODUCT WILL BE ACHIEVED.

11. INDEMNIFICATION; LIMITATION OF LIABILITY; INSURANCE

11.1 Indemnification by Ono. Ono shall indemnify, hold harmless, and defend Karyopharm, its Related Parties, and their respective directors, officers, employees, agents and representatives (collectively, the "**Karyopharm Indemnitees**") from and against any and all Losses to the extent arising out of or resulting from, directly or indirectly, (a) any breach of, or inaccuracy in, any representation or warranty made by Ono in this Agreement, or any breach or violation of any covenant or agreement of Ono in or in the performance of this Agreement, (b) the negligence or willful misconduct of Ono Indemnitees, in the performance of Ono's obligations under this Agreement, or (c) the Development, Manufacture, having Manufactured, use or Commercialization of Licensed Compounds and Licensed Products by or on behalf of Ono Indemnitees. Additionally, it is agreed between Karyopharm and Ono that (i) the indemnification language described in Schedule 11.1 shall be incorporated in the Clinical Supply Agreement (and the Commercial Supply Agreement, if any) and (ii) Ono will owe and perform indemnification obligation under the Clinical Supply Agreement (and the Commercial Supply Agreement, if any). Ono shall have no obligation to indemnify, hold harmless and defend the Karyopharm Indemnitees to the extent that Karyopharm is obligated to indemnify, hold harmless and defend Ono Indemnitees under Section 11.2.

11.2 Indemnification by Karyopharm. Karyopharm shall indemnify, hold harmless, and defend Ono, its Related Parties and their respective directors, officers, employees, agents and representatives (collectively, the "**Ono Indemnitees**") from and against any and all Losses to the extent arising out of or resulting from, directly or indirectly, (a) any breach of, or inaccuracy in, any representation or warranty made by Karyopharm in this Agreement, or any breach or violation of any covenant or agreement of Karyopharm in or in the performance of this Agreement, (b) the negligence or willful misconduct of Karyopharm Indemnitees, in the performance of Karyopharm's obligations under this Agreement, or (c) the Development, Manufacture, having Manufactured, use or Commercialization of Licensed Compounds and Licensed Products by or on behalf of Karyopharm Indemnitees. Additionally, it is agreed between Karyopharm and Ono that (i) the indemnification language described in Schedule 11.1 shall be incorporated in the Clinical Supply Agreement (and the Commercial Supply Agreement, if any) and (ii) Karyopharm will owe and perform indemnification obligation under the Clinical Supply Agreement (and the Commercial Supply Agreement, if any). Karyopharm shall have no obligation to indemnify, hold harmless and defend the Ono Indemnitees to the extent that Ono is obligated to indemnify, hold harmless and defend Karyopharm Indemnitees under Section 11.1.

11.3 Indemnification Procedure. In the event of any such claim against any Ono Indemnitee or Karyopharm Indemnitee (individually, an "**Indemnitee**"), the indemnified Party shall promptly notify the other Party in writing of the claim and the indemnifying Party shall manage and control, at its sole expense, the defense of the claim and its settlement. The indemnifying Party may settle the claim only with the consent of the applicable Indemnitees, which shall not be unreasonably withheld, conditioned or delayed; provided that an Indemnitee shall have no obligation to consent to any settlement of any such claim which imposes on such Indemnitee any liability or obligation which cannot be assumed and performed in full by the indemnifying Party. The applicable Indemnitee shall cooperate with the indemnifying Party and may, at its option and expense, be represented in any such action or proceeding. No Indemnitee may settle any such claim without the prior written consent of the indemnifying Party, which shall not be unreasonably withheld, delayed or conditioned. The indemnifying Party shall not be liable for any settlements, litigation costs or expenses incurred by any Indemnitee without the indemnifying Party's written consent. Notwithstanding the foregoing, if the indemnifying Party believes that any of the exceptions to its obligation of indemnification of the Indemnitees set forth in Sections 11.1 or 11.2 may apply, the indemnifying Party shall promptly notify the Indemnitees, which shall then have the right to be represented in any such action or proceeding by separate counsel at their expense; provided that the indemnifying Party shall be responsible for payment of such expenses if the Indemnitees are ultimately determined to be entitled to indemnification from the indemnifying Party for the matters to which the Indemnitee notified the indemnifying Party of the application of Sections 11.1 or 11.2, as applicable.

11.4 Limitation of Liability. NEITHER PARTY WILL BE LIABLE FOR SPECIAL, INCIDENTAL, CONSEQUENTIAL OR PUNITIVE DAMAGES ARISING OUT OF OR RELATING OT THIS AGREEMENT OR THE EXERCISE OF ITS RIGHTS HEREUNDER, OR LOST PROFITS ARISING FROM OR RELATING TO THIS AGREEMENT, REGARDLESS OF ANY NOTICE OF SUCH DAMAGES, EXCEPT AS A RESULT OF SUCH PARTY'S WILLFUL MISCONDUCT OR GROSS NEGLIGENCE OR A BREACH OF SECTION 7.3 OR ARTICLE 9. NOTHING IN THIS SECTION 11.4 IS INTENDED TO LIMIT OR RESTRICT THE INDEMNIFICATION RIGHTS OR OBLIGATIONS OF EITHER PARTY.

11.5 Insurance. Either Party shall, at its own expense, procure and maintain product liability insurance or self-insurance in the amount sufficient to perform its obligation hereunder. Upon the other Party's request, a Party shall promptly provide the other Party with copies of certificates of insurance evidencing such coverage.

12. INTELLECTUAL PROPERTY OWNERSHIP, PROTECTION AND RELATED MATTERS; BRAND NAME

12.1 Inventorship. For purposes of Section 12.2, inventorship for inventions and discoveries first made during the course of the performance of activities pursuant to this Agreement shall be determined in accordance with U.S. Patent Law for determining inventorship.

12.2 Ownership. Karyopharm shall own the entire right, title and interest in and to all inventions and discoveries (and Patent Rights claiming patentable inventions therein) first made or discovered solely by directors, officers or employees of Karyopharm or its Affiliates, or acquired solely by Karyopharm or its Affiliates. Ono shall own the entire right, title and interest in and to all inventions and discoveries (and Patent Rights claiming patentable inventions therein) first made or discovered solely by directors, officers or employees of Ono or its Affiliates, or acquired solely by Ono or its Affiliates. The Parties shall jointly own any Joint IP.

12.3 Disclosure. Each Party shall promptly disclose to the other Party Joint IP and all inventions made by a director, an officer or an employee of such Party or its Affiliates in the performance of its obligations under this Agreement.

12.4 Prosecution and Maintenance of Patent Rights.

12.4.1 Ono Technology.

(a) Subject to Section 12.4.1(b), Ono has the sole responsibility to, at Ono's discretion and expense, file, prosecute, and maintain all Patent Rights comprising Ono Technology (other than Joint Patent Rights), in Ono's name.

(b) In the event that Ono elects not to seek or continue to seek or maintain patent protection on any Ono Patent Rights in any country in the Karyopharm Territory, Karyopharm shall have the right (but not the obligation), at its expense, to seek, prosecute and maintain patent protection on such Ono Patent Rights in such country in the name of Ono. Ono shall use Commercially Reasonable Efforts to make available to Karyopharm and its authorized attorneys, agents or representatives, such of its employees as are reasonably necessary to assist Karyopharm in obtaining and maintaining the patent protection described under this Section 12.4.1(b). Ono shall sign or use Commercially Reasonable Efforts to have signed all legal documents necessary for Karyopharm to file and prosecute such patent applications or to obtain or maintain such patents.

12.4.2 Karyopharm Technology.

(a) Subject to Section 12.4.2(b), Karyopharm has the sole responsibility to, at Karyopharm's discretion and expense, file, conduct prosecution, and maintain, all Patent Rights comprising Karyopharm Technology (other than Joint Patent Rights), in Karyopharm's name. Karyopharm shall prosecute and maintain the Karyopharm Patent Rights in the Ono Territory.

(b) Notwithstanding Section 12.4.2(a), Karyopharm shall consult with Ono on the preparation, filing, prosecution, and maintenance of all Karyopharm Patent Rights in the Ono Territory. Karyopharm shall furnish Ono with copies of proposed filings and documents received from or filed with the relevant patent offices with respect to Karyopharm Patent Rights and such other documents directly related to the prosecution and maintenance of Karyopharm Patent Rights in the Ono Territory reasonably necessary for Ono to exercise its rights under this Section 12.4.2(b), and, as applicable, in sufficient time prior to filing such document or making any payment due thereunder to allow for review and comment by Ono and shall consider in good faith timely comments from Ono thereon.

(c) In the event that Karyopharm elects not to seek or continue to seek or maintain patent protection on any Karyopharm Patent Right in any country in the Ono Territory, Ono shall have the right (but not the obligation), at its expense, to seek, prosecute and maintain patent protection on such Karyopharm Patent Right in such country in the Ono Territory in the name of Karyopharm. Karyopharm shall use Commercially Reasonable Efforts to make available to Ono and its authorized attorneys, agents or representatives, such of its employees as are reasonably necessary to assist Ono in obtaining and maintaining the patent protection described under this Section 12.4.2(c). Karyopharm shall sign or use Commercially Reasonable Efforts to have signed all legal documents necessary for Ono to file and prosecute such patent applications or to obtain or maintain such patents. Such Karyopharm Patent Right in such country shall not be taken into account in determining the Royalty Term.

12.4.3 Joint Patent Rights.

(a) Upon receiving notice of the creation of Joint Patent Rights, the IP Working Group shall determine which Party will be responsible of obtaining and maintaining Joint Patent Rights. Such Party (the "**Joint IP Prosecuting Party**") shall file, prosecute, and maintain all Joint Patent Rights throughout the world, in the names of both Karyopharm and Ono. The Joint IP Prosecuting Party shall provide the other Party an opportunity to review and comment on material documents related to such filing, prosecution and maintenance in accordance with this Section 12.4.3, which comments the Joint IP Prosecuting Party shall consider in good faith. Each Party shall at its own cost, sign, or use Commercially Reasonable Efforts to have signed, all legal documents necessary to file and prosecute patent applications or to obtain or maintain patents in respect of such Joint Patent Rights.

(b) In the event that the Joint IP Prosecuting Party elects not to file or continue to prosecute or maintain patent protection on any Joint Patent Rights anywhere in the world, the other Party shall have the right (but not the obligation) to file, prosecute and maintain Joint Patent Rights in the names of both Karyopharm and Ono. If such other Party exercises such

right, the Joint IP Prosecuting Party shall use Commercially Reasonable Efforts to make available to such other Party and its authorized attorneys, agents or representatives, such of its employees as are reasonably necessary to assist such other Party in obtaining and maintaining the patent protection described under this Section 12.4.3(b). Each Party shall at its own cost, sign or use Commercially Reasonable Efforts to have signed all legal documents necessary to file and prosecute such patent applications or to obtain or maintain such patents.

(c) The Parties shall [**] incurred for the common activities for patent filing, prosecution and maintenance of Joint Patent Rights and each Party shall be responsible for other costs for patent filing, prosecution and maintenance of Joint Patent Rights in its Territory (collectively, "**Joint Patent Costs**"). The Joint IP Prosecuting Party shall invoice the other Party such Joint Patent Costs which shall be incurred by the other Party in accordance with this Section 12.4.3(c) within [**] after the Calendar Quarter in which such Joint Patent Costs were incurred and the other Party shall pay such Joint Patent Costs within [**] after receipt of such invoice.

(d) Notwithstanding Section 12.4.3(c), if a Party does not wish to bear Joint Patent Costs which shall be incurred by such Party with respect to a Joint Patent Right in any country(ies), such Party may, by providing [**] prior written notice to the other Party, terminate its obligation to pay such Joint Patent Costs. Such Party shall promptly assign all of its right, title and interest in and to such Joint Patent Right in such country(ies) to the other Party upon such other Party's written request.

12.4.4 Cooperation. Each Party shall: (a) use Commercially Reasonable Efforts to make its employees, agents and consultants reasonably available to the other Party (or to the other Party's authorized attorneys, agents or representatives), to the extent reasonably necessary to enable such other Party to undertake patent prosecution in accordance with this Agreement; and (b) provide the other Party with copies of all material correspondence pertaining to prosecution with the patent offices wherever applicable to Patent Rights licensed to such other Party in such other Party's Territory under this Agreement.

12.5 Enforcement.

12.5.1 Notices. Each Party shall promptly report in writing to the other Party any (a) known or suspected infringement (including any interference, opposition or invalidation proceedings) of any Karyopharm Technology, Ono Technology or Joint IP or (b) unauthorized use or misappropriation of any Confidential Information or Know-How of a Party, by a Third Party of which it becomes aware in its Territory, in each case to the extent such infringing, unauthorized or misappropriating activities involve, as to a Licensed Product or a competing product in the Field ("**Competitive Infringement**"), and shall provide the other Party with all available evidence of such Competitive Infringement.

12.5.2 Rights to Enforce.

(a) **In the Karyopharm Territory; Ono Technology.**

(i) **First Right**. Karyopharm shall have the first right to initiate an infringement or other appropriate suit or action in the Karyopharm Territory against any Third Party with respect to any Competitive Infringement in the Karyopharm Territory of any Ono Technology with respect to a product competing with a Licensed Product in the Karyopharm Territory.

(ii) **Step-In Right.** If within [**] (or such shorter period of time as required by applicable Law to avoid loss of material enforcement rights) after Karyopharm's receipt of a notice from Ono or notifying Ono of a Competitive Infringement with respect to any Ono Technology, with respect to a product competing with a Licensed Product in the Karyopharm Territory, Karyopharm does not take any action as described in Section 12.5.2(a)(i) and permitted hereunder against such Competitive Infringement in the Karyopharm Territory, Ono may in its sole discretion (but not the obligation), bring and control any legal or other appropriate action in connection therewith at its sole expense.

(b) **In the Ono Territory; Ono Technology.**

(i) **First Right**. Ono shall have the first right to initiate an infringement or other appropriate suit or action in the Ono Territory against any Third Party with respect to any Competitive Infringement in the Ono Territory of any Ono Technology with respect to a product competing with a Licensed Product in the Ono Territory.

(ii) **Step-In Right.** If within [**] (or such shorter period of time as required by applicable Law to avoid loss of material enforcement rights) after Ono's receipt of a notice from Karyopharm or notifying Karyopharm of a Competitive Infringement with respect to any Ono Technology, with respect to a product competing with a Licensed Product in the Ono Territory, Ono does not take any action as described in Section 12.5.2(b)(i) and permitted hereunder against such Competitive Infringement in the Ono Territory, Karyopharm may in its sole discretion (but not the obligation), bring and control any legal or other appropriate action in connection therewith at its sole expense.

(c) **In the Ono Territory; Karyopharm Technology.**

(i) **First Right**. Karyopharm shall have the first right to initiate an infringement or other appropriate suit or action in the Ono Territory against any Third Party with respect to any Competitive Infringement in the Ono Territory of any Karyopharm Technology with respect to a product competing with a Licensed Product in the Ono Territory.

(ii) **Step-In Right.** If within [**] (or such shorter period of time as required by applicable Law to avoid loss of material enforcement rights) after Karyopharm's receipt of a notice from Ono or notifying Ono of a Competitive Infringement with respect to any Karyopharm Technology, with respect to a product competing with a Licensed Product in the Ono Territory, Karyopharm does not take any action as described in Section 12.5.2(c)(i) and permitted hereunder against such Competitive Infringement in the Ono Territory, Ono may in its sole discretion (but not the obligation), bring and control any legal other appropriate action in connection therewith at its sole expense.

(d) **Joint IP.** In the case of any Competitive Infringement of any Joint IP, the Parties shall promptly confer to consider such Competitive Infringement and the appropriate course of action in good faith.

12.5.3 Procedures; Expenses and Recoveries. The Party having the right to initiate any infringement suit or action (including any interference, opposition or invalidation proceedings; the same hereinafter) under Section 12.5.2 above (the "**Initiating Party**") shall have the sole and exclusive right to select counsel for any such suit or action and shall pay all expenses of the suit or action, including attorneys' fees and court costs and reimbursement of the other Party's reasonable out-of-pocket expense in rendering assistance requested by the Initiating Party. Should Initiating Party initiate an infringement suit or action under Section 12.5.2, Initiating Party agrees to discuss with the other Party ways to manage the potential risk to the other Party's Patent Rights in connection with such suit or action, including limiting the number and scope of claims that are asserted in connection with such suit or action. Initiating Party shall use good faith efforts to employ any reasonable measures agreed to by the Parties to manage such potential risk. If required under applicable Law in order for the Initiating Party to initiate or maintain such suit, or if the Initiating Party is unable to initiate or prosecute such suit solely in its own name or it is otherwise advisable to obtain an effective legal remedy, the other Party shall join or participate in as a party to the suit and shall execute and cause its Affiliates to execute all documents necessary for the Initiating Party to initiate suit to prosecute and maintain such suit. In addition, at the Initiating Party's request, the other Party shall provide reasonable assistance to the Initiating Party in connection with such an infringement suit at no charge to the Initiating Party except for reimbursement by the Initiating Party of reasonable out-of-pocket expenses incurred in rendering such assistance. The non-Initiating Party shall have the right to participate and be represented in any such suit by its own counsel at its own expense. Neither Party shall enter into any settlement of any Competitive Infringement described in Section 12.5.2 that admits to the invalidity or unenforceability of the Karyopharm Patent Rights, Ono Patent Rights and Joint Patent Rights, incurs any financial or other liability on the part of the other Party or requires an admission of liability, wrongdoing or fault on the part of the other Party, in each case without the other Party's prior written consent, not to be unreasonably withheld, conditioned or delayed. If the Initiating Party obtains from a Third Party, in connection with such suit, any damages, license fees, royalties or other compensation (including any amount received in settlement of such suit), such amounts shall be allocated in all cases as follows:

(a) first, to reimburse each Party for all expenses of the suit incurred by the Parties, including attorneys' fees and disbursements, court costs and other litigation expenses (on a pro rata basis, based on each Party's respective expenses, to the extent the recovery is less than all such expenses); and

(b) second, the remainder share be retained by the Initiating Party; provided that in the case of Section 12.5.2 (c), despite of which Party is the Initiating Party, such remainder shall be retained by [**].

12.6 Infringement of Third Party Patent Rights.

12.6.1 If the Development, Manufacture, having Manufactured, use or Commercialization of any Licensed Compound and/or Licensed Product in or outside the Ono Territory pursuant to this Agreement results in a claim, suit or proceeding alleging patent infringement against Karyopharm and/or Ono (or their respective Related Parties) (collectively, "**Infringement Actions**"), the Party subject to such Infringement Actions (the "**Subject Party**") shall promptly notify the other Party in writing and shall discuss with the other Party the strategy for defending such Infringement Actions, but shall have the right to direct and control the defense thereof in its sole discretion and at its own expense, with counsel of its choice; provided that, the other Party may participate in the defense and/or settlement thereof, at its own expense with counsel of its choice. In any event, the Subject Party agrees to keep the other Party hereto reasonably informed of all material developments in connection with any such Infringement Action. Ono agrees not to settle such Infringement Action, or make any admissions or assert any position in such Infringement Action, in a manner that would adversely affect the allegedly infringing Licensed Compound and/or Licensed Product or the Development, Manufacture, having Manufactured, use or Commercialization of such Licensed Compound and/or Licensed Product in any country of the world, without the prior written consent of Karyopharm, which shall not be unreasonably withheld, delayed or conditioned; and Karyopharm agrees not to settle such Infringement Action, or make any admissions or assert any position in such Infringement Action, in a manner that would adversely affect the allegedly infringing Licensed Compound and/or Licensed Product, or the Development, Manufacture, having Manufactured, use or Commercialization of such Licensed Compound and/or Licensed Product, within the Ono Territory, without the prior written consent of Ono, which shall not be unreasonably withheld, delayed or conditioned.

12.6.2 Upon request by Ono, which shall be made within [**] following the Effective Date, Karyopharm shall use its Commercially Reasonable Efforts to clarify that Development, Manufacture, having Manufactured, use or Commercialization of the Licensed Compounds and the Licensed Products in the Field in the Ono Territory and in the Karyopharm Territory will not constitute infringement of the Patent Rights designated by Ono. Said Commercially Reasonable Efforts shall include, but are not limited to, Karyopharm's filing of opposition to the grant of patent so that the Valid Claim of the matured Patent Rights will not include Development, Manufacture, having Manufactured, use or Commercialization of the Licensed Compounds and the Licensed Products in the Field in the Ono Territory and in the Karyopharm Territory. For clarity, such action is not required until the Valid Claim in question has granted. In the case that (i) the Patent Rights (x) in any country in the Ono Territory or (y) in any

country in the Karyopharm Territory where Karyopharm Manufactures or has Manufactured the Licensed Compounds or the Licensed Products for the Ono Territory, become matured patent and (ii) Development, Manufacture, having Manufactured, use or Commercialization of the Licensed Compounds and the Licensed Products in the Field in the Ono Territory and in the Karyopharm Territory constitutes infringement of such Patent Rights, Karyopharm shall procure the patent license under the Patent Rights in the country in question at its sole cost and responsibility. If Karyopharm successfully procures patent license under the Patent Rights in the country in question, the Patent Rights shall be automatically deemed Karyopharm Technology and the license thereunder shall be granted to Ono in accordance with Section 7.1.1 (a). If Ono is required to make payment due to Karyopharm's failure to procure the license under the Patent Rights, Section 11.2 shall be applicable to said Ono's payment instead of Section 12.6.1.

12.7 Registration of License.

12.7.1 By Ono. Ono may register, in its discretion and at its expense, the licenses granted to Ono under this Agreement with the Japanese Patent Office ("Senyo-Jissiken Settei Toroku") or any other appropriate Governmental Authority in any country of the Ono Territory; provided that the Parties agree that such registration is not intended to affect the allocation of prosecution and enforcement rights and obligations set forth in Article 12. If Ono determines to make any such registrations: (a) Karyopharm agrees, at Ono's expense, to promptly take such actions and execute such documents as are reasonably requested by Ono in order to effect such registration(s) in the applicable country; and (b) in the event the licenses granted to Ono under this Agreement expire or are terminated or become non-exclusive, Ono shall promptly take such actions and execute such documents as are reasonably necessary and requested by Karyopharm to cancel such registration(s) in the applicable country with respect to the expired, terminated or revised license grant(s).

12.7.2 By Karyopharm. Karyopharm may register, in its discretion and at its expense, the licenses granted to Karyopharm under this Agreement with any appropriate Governmental Authority in any country of the Karyopharm Territory; provided that the Parties agree that such registration is not intended to affect the allocation of prosecution and enforcement rights and obligations set forth in Article 12. If Karyopharm determines to make any such registrations: (a) Ono agrees, at Karyopharm's expense, to promptly take such actions and execute such documents as are reasonably requested by Karyopharm in order to effect such registration(s) in the applicable country; and (b) in the event the licenses granted to Karyopharm under this Agreement expire or are terminated, Karyopharm shall promptly take such actions and execute such documents as are reasonably necessary and requested by Ono to cancel such registration(s) in the applicable country with respect to the expired or terminated license grant(s).

12.8 Patent Term Extensions.

12.8.1 Karyopharm shall reasonably cooperate with Ono to determine a mutually agreeable strategy to seek supplemental protection certificates ("**SPC**"), patent term extensions and restorations for Karyopharm Patent Rights, Ono Patent Rights or Joint Patent Rights in the Field in the Ono Territory, which may include seeking SPCs, extensions and restorations for Karyopharm Patent Rights, Ono Patent Rights or Joint Patent Rights in the Ono Territory, and the Parties, subject to the provisions of any Karyopharm Third Party Agreement, shall seek SPCs, extensions and restorations for the Karyopharm Patent Rights, Ono Patent Rights or Joint Patent Rights in the Ono Territory in accordance with that strategy. Where required under national Law, Karyopharm shall make the filings for such SPCs, extensions and restorations for Karyopharm Patent Rights, Ono Patent Rights or Joint Patent Rights in the Ono Territory in accordance with this Section 12.8.1. Each Party shall execute such authorizations and other documents and take such other actions as may be reasonably requested by the other Party to obtain any such SPCs, extensions and restorations for Karyopharm Patent Rights, Ono Patent Rights or Joint Patent Rights in the Ono Territory.

12.8.2 Ono shall reasonably cooperate with Karyopharm to determine a mutually agreeable strategy to seek SPCs, patent term extensions and restorations for Ono Patent Rights or Joint Patent Rights in the Field in the Karyopharm Territory, which may include seeking SPCs, extensions and restorations for Ono Patent Rights or Joint Patent Rights in the Karyopharm Territory, and the Parties shall seek SPCs, extensions and restorations for the Ono Patent Rights or Joint Patent Rights in the Karyopharm Territory in accordance with that strategy. Where required under national Law, Ono shall make the filings for such SPCs, extensions and restorations for Ono Patent Rights or Joint Patent Rights in the Karyopharm Territory in accordance with this Section 12.8.2. Each Party shall execute such authorizations and other documents and take such other actions as may be reasonably requested by the other Party to obtain any such SPCs, extensions and restorations for Ono Patent Rights or Joint Patent Rights in the Karyopharm Territory.

12.9 Brand Name

12.9.1 Brand Name of the Product. Both Parties acknowledge and agree that Commercialization of the Licensed Product under a common brand name or trademark throughout the world would be beneficial for both Parties in order to maximize the value of the Licensed Product. In furtherance of the foregoing, each Party shall have the right (but not the obligation) to propose to the other Party a limited number of brand names under consideration for use in Commercializing the Licensed Product and shall consider in good faith any

comments the other Party has on such brand names. If the Parties select one brand name for, or a Party selects the same brand name that the other Party has decided to use, in Commercializing the Licensed Product (the "**Common Brand Name**"), then, subject to successful registration and approval of such Common Brand Name by the applicable Governmental Authorities, each Party shall use such Common Brand Name for Commercialization of the Licensed Product in its respective Territory. Karyopharm shall search the possibility of the registration worldwide, and if confirmed the possibility shall file the application for registration of the trademark rights for the Common Brand Name using counsel of its own choice at Karyopharm's cost for the Karyopharm Territory and Ono's cost for the Ono Territory. After registration, Karyopharm shall assign the rights to the Common Brand Name in the Ono Territory to Ono without requiring Ono any compensation for such assignment. The costs of procedure related to such assignment shall be borne by [**]. Karyopharm shall be responsible for the prosecution, registration and maintenance of such trademark rights in the Karyopharm Territory at Karyopharm's sole costs. Karyopharm shall be responsible for the prosecution and registration of such trademark rights in the Ono Territory at Ono's sole costs, and Ono shall be responsible for the maintenance of such trademark rights in the Ono Territory at Ono's sole costs.

12.9.2 If the Parties do not reach an agreement on a Common Brand Name, each Party may use, for Commercializing the Licensed Product in countries in each Party's respective Territory, its own trademark it considers appropriate and which is reasonably suitable for the Licensed Product in such countries. Both Parties shall own respectively all rights, title and interests in and to its own trademarks throughout the world and shall have the sole right to register, prosecute and maintain its trademarks using counsel of its own choice and at its own expense.

13. TERM AND TERMINATION

13.1 **Term.** This Agreement shall be effective as of the Effective Date and, unless terminated earlier, this Agreement shall continue in effect on a Licensed Product-by-Licensed Product and country-by-country basis until expiration of the last Royalty Term to expire under this Agreement ("**Term**"). Upon expiration of this Agreement on a Licensed Product-by-Licensed Product and country-by-country basis, Ono's license pursuant to Section 7.1.1 shall become a fully paid-up, irrevocable, perpetual license, sublicensable without restriction on a Licensed Product-by-Licensed Product and country-by-country basis.

13.2 **Termination by Ono**

13.2.1 **Termination without Cause**. At any time, Ono shall have the right to terminate this Agreement, on a Licensed Product-by-Licensed Product and country-by-country basis, by upon one hundred and eighty (180) days advance written notice to Karyopharm.

13.2.2 Termination for Safety or Efficacy Reason. Ono shall have the right to terminate this Agreement, on a Licensed Product-by-Licensed Product basis, for safety or efficacy reasons upon thirty (30) days written notice to Karyopharm or within a shorter period if required under applicable Law.

13.3 Termination by Either Party

13.3.1 Termination for Cause. This Agreement may be terminated at any time during the Term upon written notice by either Party if the other Party is in material breach of its obligations hereunder and has not cured such breach within [**] in the case of a payment breach, or within [**] in the case of all other breaches, after notice requesting cure of the breach.

13.3.2 Termination Upon Bankruptcy. Either Party may immediately terminate this Agreement if, at any time, the other Party becomes insolvent or an order is made or a resolution passed for the administration, winding-up or dissolution of such other Party (other than for the purposes of a solvent amalgamation or reconstruction) or an administrative or other receiver, manager, liquidator, administrator, trustee or similar officer is appointed over all or any substantial part of the assets of such other Party or such other Party enters into or proposes any composition or arrangement with its creditors generally or anything analogous to the foregoing occurs in any applicable jurisdiction.

13.4 Termination by Karyopharm for Challenges of Patent Rights. If during the Term Ono or any of its Related Party (a) commences or participates in any action or proceeding (including any patent opposition, re-examination or invalidation proceeding), or otherwise asserts any claim, challenging or denying the validity or enforceability of any Karyopharm Patent Right or any claim thereof or (b) assists any Person in bringing or prosecuting any action or proceeding (including any patent opposition, re-examination or invalidation proceeding) challenging or denying the validity or enforceability of any Karyopharm Patent Right or any claim thereof (each of (a) and (b), a "**Patent Challenge**"), then, to the extent permitted by Law, Karyopharm shall have the right, in its sole discretion, to give at least thirty (30) days prior written notice to Ono that Karyopharm may terminate this Agreement, and, unless Ono or such Related Party withdraws or causes to be withdrawn all such challenge(s) (or in the case of *ex-parte* proceedings, multi-party proceedings, or other Patent Challenges that Ono or Ono's Related Party do not have the power to unilaterally withdraw or cause to be withdrawn, Ono and Ono's Related Party ceases actively assisting any other party to such Patent Challenge and, to the extent Ono or a Ono Related Party is a party to such Patent Challenge, it withdraws from such Patent Challenge) within thirty (30) days after Ono's receipt of notice regarding such Patent Challenge, Karyopharm will have the right to terminate this Agreement by providing written notice thereof to Ono.

13.5 Effect of Termination.

13.5.1 Termination by Ono Under Section 13.3. Without limiting any other legal or equitable remedies that either Party may have, if this Agreement is terminated by Ono pursuant to Section 13.3, then the provisions of Section 13.5.1(a)-(d) shall apply:

(a) the license grants to Ono shall terminate;

(b) If such termination occurs prior to the date of the First Commercial Sale of a Licensed Product in Japan, Karyopharm shall pay Ono a royalty of [**] percent ([**]%) of net sales (with the same meaning as "Net Sales", *mutatis mutandis*) of Licensed Product by Karyopharm or its Related Parties in the Ono Territory, and the provisions of Sections 8.4.2 through 8.11 and the defined terms therein shall apply, *mutatis mutandis*, with the references to "Karyopharm" and "Ono" switched;

(c) If such termination occurs on or after the date of the First Commercial Sale of a Licensed Product in Japan, Karyopharm shall pay Ono a royalty of [**] percent ([**]%) of net sales (with the same meaning as "Net Sales", *mutatis mutandis*) of Licensed Product by Karyopharm or its Related Parties in the Ono Territory, and the provisions of Sections 8.4.2 through 8.11 and the defined terms therein shall apply, *mutatis mutandis*, with the references to "Karyopharm" and "Ono" switched; and

(d) the license grants to Karyopharm in Section 7.1.2 shall become a non-transferable (except as provided in Section 14.1), sublicenseable (including through multiple tiers) (subject to Section 7.2), non-exclusive, royalty-bearing license, and shall be expanded to include the Ono Territory.

13.5.2 Termination by Karyopharm Under Section 8.10, 13.3 or 13.4; Termination by Ono Under Section 13.2 or Termination Upon Mutual Written Agreement of the Parties. Without limiting any other legal or equitable remedies that either Party may have, if this Agreement is terminated by Karyopharm pursuant to Sections 8.10, 13.3 or 13.4, or by Ono pursuant to Section 13.2, or upon the mutual written agreement of the Parties, then the provisions of Section 13.5.2(a)-(k) shall apply:

(a) Upon termination notice from terminating Party to the other Party or mutual agreement for termination, as applicable, Ono shall responsibly wind-down any on-going Development, Manufacture, having Manufactured, use or Commercialization of the Licensed Compound or the Licensed Product. Ono shall be responsible for [**];

(b) the license grants to Ono shall terminate, and the license grants to Karyopharm in Section 7.1.2 (i) specific to the Licensed Compound or Licensed Product shall survive on a perpetual and irrevocable basis and (ii) not specific to the Licensed Compound or Licensed Product shall become a non-transferable (except as provided in Section 14.1), sublicenseable (including through multiple tiers) (subject to Section 7.2), non-exclusive, royalty-bearing license, and each license for (i) and (ii) shall be expanded to include the Ono Territory;

(c) Ono shall provide to Karyopharm a fair and accurate description of the status of the Development, Manufacture, use and Commercialization of the Licensed Product in the Field in the Ono Territory as of the effective date of termination;

(d) Ono shall as promptly as practicable transfer to Karyopharm or Karyopharm's designee, to the extent practicable and necessary for Karyopharm or its Related

Parties to Develop, Manufacture, have Manufactured, use or Commercialize the Licensed Compound and Licensed Product in the Ono Territory, (i) possession and ownership of all filings and approvals (including all INDs, NDAs, Regulatory Approvals and pricing and reimbursement approvals) relating to the Development, Manufacture, use or Commercialization of the Licensed Product, (ii) copies of data, reports, records and materials, and other sales and marketing related information Controlled by Ono, including non-clinical and Clinical Data relating to the Licensed Product and all adverse event data Controlled by Ono; provided that Ono shall use Commercially Reasonable Efforts to obtain for Karyopharm the right to access such data, reports, records, materials, and other sales and marketing related information, and (iii) records and materials in Ono's possession containing Confidential Information of Karyopharm requested to be transferred by Karyopharm;

(e) if the effective date of termination is after the First Commercial Sale of the Licensed Product in any country in the Ono Territory, then, subject to Karyopharm's election and subject to applicable Laws, Ono shall (i) appoint Karyopharm's designee as its exclusive distributor of the Licensed Product in the Ono Territory and grant Karyopharm the right to appoint sub-distributors, or (ii) continue to distribute the Licensed Product in the Ono Territory, until such time as all Regulatory Approvals in the Ono Territory have been transferred to Karyopharm or its designee, and in the case of (ii), the license granted to Ono under Section 7.1.1 shall survive to the extent necessary to perform Ono's obligation under this Section 13.5.2 (e);

(f) if Ono or its Related Parties are Manufacturing the Licensed Product, then, except for the termination pursuant to Section 13.2.2, at Karyopharm's option, Ono shall supply the Licensed Product to Karyopharm in the Ono Territory at (A) [**]; or (B) [**], in each case (A) or (B) plus [**] percent ([**]%) thereof , until the earlier of (i) such time as all Regulatory Approvals in the Ono Territory have been transferred to Karyopharm or its designee, Karyopharm has obtained all necessary manufacturing approvals and Karyopharm has procured or developed its own source of the Licensed Product supply for the Ono Territory or (ii) [**] following the effective date of such termination;

(g) if Karyopharm so requests, and to the extent permitted under Ono's or any of its Affiliates' obligations to Third Parties at the time of termination, Ono shall use Commercially Reasonable Efforts to transfer to Karyopharm any Third Party agreements relating solely and exclusively to the Development, Manufacture or Commercialization of the Licensed Product to which Ono or any of its Affiliates is a party, subject to any required consents of such Third Party;

(h) Ono shall promptly transfer and assign to Karyopharm all of [**] used in Commercialization of the Licensed Product (but not any Ono house marks or any trademark containing the word "Ono" owned by Ono);

(i) Ono shall, upon Karyopharm's written request, transfer to Karyopharm any inventory of Licensed Compounds and Licensed Products owned or controlled by Ono or its Affiliates as of the termination date at the (i) [**] for such Licensed Products or (ii) [**] for such supply, as applicable;

(j) Ono shall provide any other assistance reasonably requested by Karyopharm for the purpose of allowing Karyopharm or its designee to proceed expeditiously with the Development, Manufacture, use and Commercialization of Licensed Compounds and Licensed Products in or for the Ono Territory for [**] from the effective date of termination of this Agreement; and

(k) Ono shall execute all documents and take all such further actions as may be reasonably requested by Karyopharm in order to give effect to the foregoing clauses.

13.5.3 Bankruptcy. All rights and licenses granted under or pursuant to this Agreement by a Party to the other Party, including those set forth in Section 7.1, are and shall otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The Parties agree that the Parties and their respective permitted Sublicensees or sublicensees, as Sublicensees or sublicensees of such rights under this Agreement, shall retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code and any foreign counterpart thereto.

13.6 Effect of Expiration or Termination; Survival. Any expiration or termination of this Agreement shall be without prejudice to the rights of either Party against the other accrued or accruing under this Agreement prior to expiration or termination, including Articles 1, Article 8 (with respect to milestone payments and royalty payments accruing prior to, but not yet paid, as of the effective date of termination), 11, and 14 and Sections 4.5, 7.3.2, 7.4, 8.6, 8.7, 9.1, 9.2 (to the extent Confidential Information is included in a proposed disclosure), 10.5, 12.6, 12.7, 13.1, 13.5, 12.4.3, 12.4.4, and 13.6 which shall survive any expiration or termination of this Agreement. Except as otherwise set forth in this Article 13, upon termination or expiration of this Agreement all rights and obligations of the Parties under this Agreement will cease.

14. MISCELLANEOUS

14.1 Assignment / Change in Control. This Agreement may not be assigned or otherwise transferred, nor may any right or obligation hereunder be assigned or transferred, by either Party without the written consent of the other Party; provided, however, that either Party may, without the other Party's written consent, assign this Agreement and its rights and obligations hereunder in whole or in part to (a) an Affiliate; or (b) the relevant Person in the context of a Change in Control. Each Party agrees that, notwithstanding any provisions of this Agreement to the contrary, (A) no Patent Right, Know-How or other intellectual property or other proprietary rights not Controlled by a Party prior to a Change in Control with respect to such Party or by any of its Affiliates who were its Affiliates prior to such Change in Control (such Party's "**Pre-Existing Affiliates**"), or which first becomes Controlled by such Party's Pre-Existing Affiliates following such Party's Change in Control, will be deemed Controlled by such Party or its Affiliates for purposes of this Agreement after such Change in Control, other than any Patent Right that claims priority, directly or indirectly, to any other Patent Right first Controlled by such Party or its Pre-Existing Affiliates before such Change in Control and licensed to the other Party hereunder as of such Change in Control, which will be deemed Controlled by such Party or its Pre-Existing Affiliates thereafter no matter when such Patent Right is filed or issued, and (B) to

the extent that certain Person, who starts to control Karyopharm as the result of Change in Control, is developing or commercializing any [**] in the Field, any Development and Commercialization of a Licensed Product in combination with [**] by the Parties shall be conducted subject to appropriate firewall procedures to segregate such activities (and the personnel conducting such activities) from the activities performed by or on behalf of such Person with respect to any [**] it is developing or commercializing, to ensure that [**] is disclosed to employees of such Person, who are developing or commercializing such Person's [**]. Any purported assignment in violation of this Section 14.1 shall be void. For purposes of this Section 14.1, "**Change in Control**" means, with respect to a Party (a) the acquisition of beneficial ownership, directly or indirectly, by any Third Party of securities or other voting interest of such Party representing a majority or more of the combined voting power of such Party's then outstanding securities or other voting interests, (b) any merger, reorganization, consolidation or business combination involving such Party with a Third Party that results in the holders of beneficial ownership (other than by virtue of obtaining irrevocable proxies) of the voting securities or other voting interests of such Party (or, if applicable, the ultimate parent of such Party) immediately prior to such merger, reorganization, consolidation or business combination ceasing to hold beneficial ownership of more than (50%) of the combined voting power of the surviving entity immediately after such merger, reorganization, consolidation or business combination, or (c) any sale, lease, exchange, contribution or other transfer (in one transaction or a series of related transactions) of all or substantially all of the assets of such Party to which this Agreement relates to a Third Party, other than a sale or disposition of such assets to an Affiliate of such Party.

14.2 Governing Law. This Agreement shall be construed and the respective rights or obligations of the Parties determined in accordance with the substantive Law of the State of New York, other than (a) its conflicts of laws principles; (b) the United Nations Convention on Contracts for the International Sale of Goods; (c) the 1974 Convention on the Limitation Period in the International Sale of Goods (the "**1974 Convention**"); and (d) the Protocol amending the 1974 Convention, done at Vienna April 11, 1980; provided, that with respect to matters involving enforcement of intellectual property rights, the Law of the applicable country shall apply.

14.3 Arbitration.

14.3.1 Subject to Section 14.3.4, any disputes, claims or controversies in connection with this Agreement, including any questions regarding its formation, existence, validity, enforceability, performance, interpretation, tort, breach or termination hereof ("**Disputes**"), shall be resolved amicably by negotiation between the Parties. Either Party may initiate such informal Dispute resolution by sending written notice of the Dispute to the other Party, and then appropriate representatives of the Parties shall meet for attempted resolution by good faith negotiations in person or via video-conference without delay from such notice. If such representatives are unable to resolve such Disputes within [**] of such notice, either Party may refer the matter by written notice to the Executive Officers for discussion and resolution. If such Executive Officers are unable to resolve such Dispute within [**] of such written notice, Section 14.3.2 shall apply.

14.3.2 All Disputes which remain unresolved under Section 14.3.1 shall be finally resolved under the Rules of Arbitration of the International Chamber of Commerce by three (3) arbitrators appointed in accordance with the said rules. Each Party shall nominate one (1) arbitrator, and the two (2) arbitrators so nominated shall nominate a third arbitrator, who shall act as the chairperson. The place of the arbitration shall be Boston, Massachusetts if the arbitration is demanded by Ono, and Osaka, Japan if the arbitration is demanded by Karyopharm. The language of the arbitration shall be English. If the tribunal orders production of documents, the tribunal shall take guidance from the IBA Rules on the Taking of Evidence in International Arbitration as current on the date of the commencement of the arbitration. The costs and expenses of translation of relevant documents and translators relating to the arbitration shall be deemed as the costs and expenses of the arbitration, and may be allocated to any Party in the award by the tribunal. The tribunal may include in its award an allocation to any Party of costs and expenses relating to the arbitration, excluding lawyers' fee, as the tribunal deems reasonable. Each Party shall bear its own cost and expenses for its own lawyers. The award rendered by the tribunal shall be final and binding upon the Parties and may be entered in any court of appropriate jurisdiction. The Emergency Arbitrator Provisions and the Expedited Procedure Provisions shall not apply.

14.3.3 The existence and content of the arbitral proceedings, any information exchanged between Parties during the arbitral proceedings and any rulings or award shall be kept confidential by the Parties and members of the tribunal except (a) to the extent that disclosure may be required by a Party to fulfill a legal duty, protect or pursue a legal right, or enforce or challenge an award in bona fide legal proceedings before a court or other judicial authority, (b) with the consent of both Parties, (c) where needed for the preparation or presentation of a claim or defense in this arbitration, (d) where such information is already in the public domain other than as a result of a breach of this clause, or (e) by order of the tribunal upon application of a Party.

14.3.4 At any time, a Party may seek or obtain preliminary, interim or conservatory measures from the arbitrators or from a court.

14.3.5 Unless otherwise agreed by the Parties, a dispute between the Parties relating to the validity or enforceability of any Patent Right regarding this Agreement shall not be subject to arbitration and shall be submitted to a court or patent office of competent jurisdiction in the relevant country in which such patent was issued or, if not issued, in which the underlying patent application was filed. The Parties submit to the jurisdiction of such court or patent office and irrevocably waive any assertion that the case should be heard in a different venue or forum.

14.4 Entire Agreement; Amendments. This Agreement contains the entire understanding of the Parties with respect to the subject matter hereof, and supersedes all previous arrangements with respect to the subject matter hereof, whether written or oral, including the Prior CDA. This Agreement (including the Schedules hereto) may be amended, or any term hereof modified, only by a written instrument duly-executed by authorized representatives of both Parties.

14.5 Severability. If any provision hereof should be held invalid, illegal or unenforceable in any respect in any jurisdiction, the Parties shall substitute, by mutual consent, valid, legal and enforceable provisions for such invalid, illegal or unenforceable provisions, which valid, legal and enforceable provisions in their economic effect are sufficiently similar to the invalid, illegal or unenforceable provisions that it can be reasonably assumed that the Parties would have entered into this Agreement with such valid, legal and enforceable provisions. In case such valid, legal and enforceable provisions cannot be agreed upon, the invalid, illegal or unenforceable of one or several provisions of this Agreement shall not affect the validity of this Agreement as a whole.

14.6 Headings. The captions to the Articles and Sections hereof are not a part of this Agreement and shall not affect in any way the meaning or interpretation of this Agreement, but are merely for convenience to assist in locating and reading the several Articles and Sections hereof.

14.7 Waiver of Rule of Construction. Each Party has had the opportunity to consult with counsel in connection with the review, drafting and negotiation of this Agreement. Accordingly, the rule of construction that any ambiguity in this Agreement shall be construed against the drafting Party shall not apply.

14.8 Interpretation. Except where the context expressly requires otherwise, (a) the use of any gender herein shall be deemed to encompass references to any other gender, and the use of the singular shall be deemed to include the plural (and vice versa); (b) the words “include”, “includes” and “including” shall be deemed to be followed by the phrase “without limitation” and shall not be interpreted to limit the provision to which it relates; (c) the word “will” shall be construed to have the same meaning and effect as the word “shall”; (d) any definition of or reference to any agreement, instrument or other document herein shall be construed as referring to such agreement, instrument or other document as from time to time amended, supplemented or otherwise modified (subject to any restrictions on such amendments, supplements or modifications set forth herein); (e) any reference herein to any Person shall be construed to include the Person’s successors and assigns (subject to Section 14.1 with respect to a Party); (f) the words “herein”, “hereof” and “hereunder”, and words of similar import, shall be construed to refer to this Agreement in its entirety and not to any particular provision hereof; (g) all references herein to Articles, Sections, Exhibits or Schedules shall be construed to refer to Articles, Sections, Exhibits or Schedules of this Agreement, and references to this Agreement include all Exhibits and Schedules hereto; (h) the word “notice” means notice in writing (whether or not specifically stated) and shall include notices, consents, approvals and other written communications contemplated under this Agreement; (i) provisions that require that a Party, the Parties or any committee hereunder “agree,” “consent” or “approve” or the like shall require that such agreement, consent or approval be specific and in writing, whether by written agreement, letter, approved minutes or otherwise (but excluding e-mail and instant messaging); (j) references to any specific Law, or article, section or other division thereof, shall be deemed to include the then-current amendments thereto or any replacement or successor Law; (k) the term “or” shall be interpreted in the inclusive sense commonly associated with the term “and/or”; (l) references to “$” or “dollars” shall mean U.S. Dollars; and (m) references to “day” shall mean a calendar day unless “Business Day” is specified.

14.9 No Implied Waivers; Rights Cumulative. Neither Party shall be deemed to have waived any of its right, power, remedy or privilege under this Agreement, or provided by statute or at law or in equity or otherwise unless the waiver is made in writing, signed by a duly authorized representative of that Party. No failure on the part of Karyopharm or Ono to exercise, and no delay in exercising, any right, power, remedy or privilege under this Agreement, or provided by statute or at law or in equity or otherwise, shall impair, prejudice or constitute a waiver of any such right, power, remedy or privilege or be construed as a waiver of any breach of this Agreement or as an acquiescence therein, nor shall any single or partial exercise of any such right, power, remedy or privilege preclude any other or further exercise thereof or the exercise of any other right, power, remedy or privilege.

14.10 Notices. All notices which are required or permitted hereunder shall be in writing and sufficient if delivered personally, sent by facsimile (and promptly confirmed by personal delivery, registered or certified mail or overnight courier), sent by internationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

If to Karyopharm, to:	Karyopharm Therapeutics Inc. Attention: Chief Executive Officer 85 Wells Avenue, Suite 210 Newton, MA 02459 Facsimile No.: [**]
With a copy to:	Karyopharm Therapeutics Inc. Attention: General Counsel 85 Wells Avenue, Suite 210 Newton, MA 02459 Facsimile No.: [**]
With a copy to:	WilmerHale LLP 60 State Street Boston, MA 02109 USA Attention: Steven D. Singer, Esq. Facsimile No.: 1-(617) 526-5000
If to Ono, to:	Ono Pharmaceutical Co., Ltd. 8-2, Kyutaromachi 1-chome, Chuo-ku, Osaka, 541-8564, Japan Attention: [**] Facsimile No.: [**]
With a copy to:	Ono Pharmaceutical Co., Ltd. Attention: [**] Facsimile No.: [**]

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such notice shall be deemed to have been given: (a) when delivered if personally delivered or sent by facsimile on a business day (or if delivered or sent on a non-business day, then on the next business day); (b) on receipt if sent by overnight courier; or (c) on receipt if sent by mail.

Notwithstanding any provision of this Section 14.10, it is understood and agreed between the Parties that this Section 14.10 is not intended to govern the day-to-day communications necessary between the Parties in performing their duties, in due course, under the terms and conditions hereof.

14.11 Compliance with Law. Each Party and its Affiliates shall conduct, and shall use Commercially Reasonable Efforts to cause its Related Parties, contractors and consultants to conduct, all of its activities contemplated under this Agreement in accordance with all applicable Laws of the country in which such activities are conducted, as well as the US Foreign Corrupt Practices Act and the UK Bribery Act 2010, and all export control and sanctions Law of the United States. In addition, each Party shall not, shall ensure that its Affiliates do not, and shall use Commercially Reasonable Efforts to cause its Related Parties, contractors and consultants not to, take any action that would cause the other Party to violate any applicable anti-corruption or sanctions Laws.

14.12 Force Majeure. Neither Party shall be held liable to the other Party nor be deemed to have defaulted under or breached this Agreement for failure or delay in performing any obligation under this Agreement to the extent that such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party, potentially including embargoes, war, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, fire, floods, earthquake, tsunami or other acts of God. The affected Party shall notify the other Party of such force majeure circumstances as soon as reasonably practical, and shall promptly undertake all reasonable efforts necessary to cure such force majeure circumstances.

14.13 Independent Contractors. It is expressly agreed that Karyopharm and Ono shall be independent contractors and that the relationship between Karyopharm and Ono shall not constitute a partnership, joint venture or agency. Karyopharm shall not have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on Ono, without the prior written consent of Ono, and Ono shall not have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on Karyopharm without the prior written consent of Karyopharm.

14.14 Counterparts. This Agreement may be executed in two (2) or more counterparts, including by facsimile or PDF signature pages, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

14.15 Binding Effect; No Third Party Beneficiaries. As of the Effective Date, this Agreement shall be binding upon and inure to the benefit of the Parties and their respective permitted successors and permitted assigns. Except as expressly set forth in this Agreement, no Person other than the Parties and their respective Affiliates and permitted successors and assignees hereunder shall be deemed an intended beneficiary hereunder or have any right to enforce any obligation of this Agreement.

[REMAINDER OF PAGE LEFT INTENTIONALLY BLANK]

IN WITNESS WHEREOF, the Parties have executed this Agreement as of the Effective Date.

ONO PHARMACEUTICAL CO., LTD.

BY: /s/ Gyo Sagara

NAME: Gyo Sagara

TITLE: President, Representative Director and CEO

KARYOPHARM THERAPEUTICS INC.

BY: /s/ Michael G. Kauffman

NAME: Michael G. Kauffman

TITLE: Chief Executive Officer

SCHEDULE 1.43

KARYOPHARM THIRD PARTY AGREEMENTS

[**]

Research Agreement, made as of the 18th day of July, 2011, by and between The Multiple Myeloma Research Foundation, Inc. and Karyopharm[1]

[**].

SCHEDULE 1.46

KPT-8602

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1. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATIONS

1.1. Physical Properties

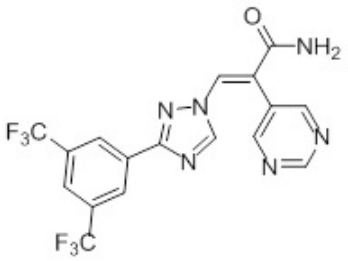
White to off-white solid, Melting point: 225 °C

1.2. Chemical Properties

1.2.1. Chemical Name

(*E*)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1*H*-1,2,4-triazol-1-yl)-2-(pyrimidin-5-yl)acrylamide

1.2.2. Structural Formula



1.2.3. Molecular Formula

$C_{17}H_{10}F_6N_6O$

1.2.4. Molecular Weight

428.30 g/mol

1.3. Solubility

< [**] mg/mL in water; ³ [**] mg/mL in dimethylsulfoxide (DMSO); < [**] mg/mL in methanol

1.4. Formulations

The clinical dosage form for KPT-8602 is an [**] for oral administration. Initial supplies came in two strengths of active ingredient: 5 mg and 20 mg of the active pharmaceutical ingredient per tablet. Additional supplies for the clinic included the addition of a 10 mg tablet based on the 5 mg formulation and are size proportional (2x) to the 5 mg tablet. All inactive ingredients used in the tablets are either compendia or generally recognized as safe. Tablets are film coated for ease in handling.

1.5. Storage Conditions

KPT-8602 tablets are packaged in [**] with an [**] and can be stored at room temperature between 5 and 25ºC. Instructions for the receipt, inspection, storage, preparation, administration, and disposal of KPT-8602 tablets are provided in the Pharmacy Manual at each clinical site.

SCHEDULE 1.74

SELINEXOR

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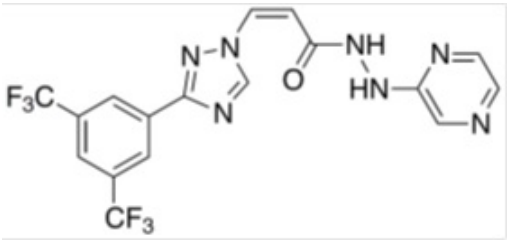
2. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATIONS

2.1. Drug Substance Description

Product Name:	Selinexor (International Nonproprietary Name [INN])
	Selinexor (United States Adopted Name [USAN])
Company Code:	KPT-330
Chemical Name:	(Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl)-1H-1,2,4-triazol-1-yl)-*N'*-(pyrazin-2-yl)acrylohydrazide
Molecular Formula:	$C_{17}H_{11}F_6N_7O$
Molecular Weight:	443.31 g/mol
Pharmacologic Class:	Apoptosis inducing agent (Wu, 2006)

Figure 1: Chemical Structure of Selinexor



2.2. Drug Product Formulation

The selinexor dosage forms used in clinical studies are capsules and tablets for oral administration. Capsule strengths for selinexor were 1 mg, 5 mg and 20 mg; tablet strengths are 10 mg and 25 mg (supplied in bottles), and 20 mg tablets (supplied in blister packs).

Capsules of selinexor for oral administration are filled with a micronized mixture containing about [**]% by weight of the active pharmaceutical ingredient (API) (selinexor), and an approximately [**] mixture of [**] (the manufacturing procedure involves [**] of the active pharmaceutical ingredient and [**]). The capsules were used in early phase 1 studies but are no longer manufactured or used.

Selinexor 10 and 25 mg tablets (tablet formulation #1) were manufactured via [**] and contain approximately [**]% by weight of the API as well as, [**]. Additional inactive excipients include [**]. The tablets are coated with [**]. These tablet components/excipients are common to oral pharmaceuticals and/or compendial. Tablet formulation #1 (1st generation tablets) has been evaluated in a Phase 1b comparative bioavailability study KCP-330-003 and demonstrated similar exposure to the capsules. Tablet strengths are distinguished by tablet size and debossing (K10, K20 and K25 for 10 mg, 20 mg, and 25 mg tablets respectively).

Selinexor 20 mg tablets (tablet formulation #2) were manufactured via [**] and contain [**]% by weight of the API as well as [**] (lubricant). Additional inactive excipients include [**] are blended with the [**], and [**]. The [**] to provide product formulation. Tablet formulation #2 (2nd generation tablets) has been evaluated in a Phase 1b comparative bioavailability study KCP-330-003 and demonstrated similar exposure to tablet formulation #1.

Twenty (20) milligram tablets (tablet formulation #2) are the preferred dosage form for current and future clinical trials. The use of the 20 mg tablets in CSTs began in December, 2014.

2.3. Storage and Handling

All selinexor formulations can be stored or shipped either at ambient temperature or refrigerated. Selinexor tablets (20 mg) are to be stored at room temperature (at or below 30°C) in clear blister strips that are composed of either [**] with a [**] or [**] with a [**]. The blistered packaged product will be placed in paperboard secondary packaging, to which labeling materials will be fixed.

SCHEDULE 2.1

Relevant Clinical Studies

Selinexor

Multiple Myeloma

1. BOSTON (Phase III trial, ongoing): Randomized, controlled, open-label study of selinexor, bortezomib, and dexamethasone versus bortezomib and dexamethasone in patients with relapsed or refractory Multiple Myeloma (rrmm).

2. STORM (Phase IIb trial, ongoing): Open-label, single-arm study of selinexor plus low dose dexamethasone in patients with multiple myeloma previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an immunomodulatory agent, a proteasome inhibitor, and the anti-CD38 mAb daratumumab.

3. STOMP (Phase I/II trial, ongoing): Assessment of the efficacy and safety of four separate combination therapies for the treatment of patients with rrmm: selinexor + pomalidomide + dexamethasone, selinexor + bortezomib + dexamethasone, selinexor + lenalidomide + dexamethasone, and selinexor + daratumumab + dexamethasone.

Non-Hodgkin’s Lymphoma

4. SADAL (Phase IIb trial, ongoing): Randomized study of selinexor (60 mg versus 100 mg) in relapsed or refractory Diffuse Large B-Cell Lymphoma (DLBCL). (in consultation with FDA, protocol amended to remove the 100 mg arm and continue enrollment in only the 60 mg twice weekly arm).

Solid Tumors

5. SEAL (Phase II/III trial, ongoing): Randomized study of selinexor vs. placebo in patients with advanced, unresectable, dedifferentiated Liposarcoma.

KPT-8602

6. Phase I/II trial (ongoing): Dose escalation clinical trial for KPT-8602 in patients with to Pancreatic Cancer, Colorectal Cancer and Myelodysplastic Syndrome.

SCHEDULE 2.2

Overview Plan

[**]

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SCHEDULE 10.2.2[2]

KARYOPHARM PATENT RIGHTS

Docket No.	Country	Application Status	Application No.	Filing Date	Publica-tion No.	Public-ation Date	Patent No. Issue Date

Confidential Materials omitted and filed separately with the Securities and Exchange Commission. A total of 3 pages were omitted. [**]

2 Current as of Sept 8, 2017

SCHEDULE 11.1

Agreed Indemnification Language to be incorporated

in the Clinical Supply Agreement (and the Commercial Supply Agreement, if any)

8.1 Supplier Indemnification. Subject to the provisions of Section 8.3 (of the Clinical Supply Agreement), Supplier (i.e. Karyopharm) shall defend, indemnify, and hold Purchaser, its Affiliates and Related Party and its and their successors, assigns, and their respective directors, officers, agents, and employees (collectively, the "Purchaser Indemnitees") harmless with respect to all liability, damage, judgments, losses and expenses (including reasonable attorneys' fees and court costs) whether for money or equitable relief, (collectively, "Losses") arising out of, relating to, or resulting from suits, proceedings, claims, actions, demands, or threatened claims, actions or demands, in each case brought by a Third Party (each, a "Claim") to the extent Claim arises out of or results from (a) bodily injury, risk of bodily injury, death, property damage or product liability arising from Supplier's failure to supply Conforming Licensed Particle (i.e. the Licensed Product or any component or intermediate thereof or a Related Substance, which satisfies the conditions set forth in representation and warranty in Section 8.1 of the Clinical Supply Agreement) at the time of Delivery to Purchaser, (b) the breach or default by Supplier of any representation, warranty, covenant, or agreement of Supplier contained in the Agreement (i.e. the Clinical Supply Agreement) or (c) the negligence, fraud, fraudulent misrepresentation or willful misconduct of Supplier in the course of the performance of its obligations hereunder, except, in each case, to the extent any such Losses result from the negligence or willful misconduct of a Purchaser Indemnitee or from the breach or default by Purchaser of any representation, warranty, or covenant of Purchaser contained in this Agreement (i.e. the Clinical Supply Agreement). It is confirmed that Supplier will give Purchaser its representation and warranty as follows: at the time of Delivery, each Licensed Particle (i.e. the Licensed Product or any component or intermediate thereof or a Related Substance) supplied under this Agreement (i.e. the Clinical Supply Agreement) (a) will have been manufactured in accordance with the Specifications, the Law as applicable to Supplier with respect to such Licensed Particle, the Agreement (i.e. the Clinical Supply Agreement), any applicable Statement of Work and the Quality Agreement; (b) will have been manufactured in accordance with cGMP if the Statement of Work pursuant to which such Licensed Particle is supplied expressly specifies that such Licensed Particle is to be manufactured in accordance with cGMP; (c) will have a shelf life equal to or exceeding the Minimum Shelf Life (it being confirmed that, in case that Licensed Particle becomes out of the Specifications in course of the post release stability study therefor, such Licensed Particle shall be deemed to fail to have a Minimum Shelf Life); (d) will comply with all applicable Laws, and will not be adulterated or misbranded, (e) will not be an article that may not be introduced into interstate commerce under the provisions of §§404 or 505 of the United States Food, Drug, and Cosmetic Act ("FD&C Act") ("Conforming Licensed Particle") and (f) upon receipt by Supplier of full payment for a Delivery of a Licensed Particle, such Licensed Particle shall be free of all Third Party liens and security interests.

8.2 Purchaser Indemnification. Subject to the provisions of Section 8.3 (of the Clinical Supply Agreement), Purchaser shall defend, indemnify and hold Supplier, its Affiliates and Related Party, and its and their successors, assigns, and their respective directors, officers, agents,

and employees (collectively, the "Supplier Indemnitees"), harmless with respect to all Losses arising out of, relating to, or resulting from Claims against a Supplier Indemnitee to the extent Claims arises out of or resulting from (a) the breach or default by Purchaser of any representation, warranty, covenant or agreement of Purchaser contained in this Agreement (i.e. the Clinical Supply Agreement); (b) the negligence or willful misconduct of Purchaser or its Representatives in the course of the performance of Purchaser's obligations hereunder; (c) the negligence of Purchaser or its Representatives in connection with the storage, handling, or use of any Licensed Particle after delivery pursuant to Section 2.5 (of the Clinical Supply Agreement); or (d) manufacture, clinical development, use, sale, import, distribution, or other exploitation of any Licensed Particle, including Claims for bodily injury, risk of bodily injury, death or property damage and product liability resulting from, arising out of or relating to any clinical trials, or other products liability claims, except, in each case, to the extent any such Losses result from the negligence or willful misconduct of a Supplier Indemnitee or from the breach or default by Supplier of any representation, warranty, or covenant of Supplier contained in this Agreement (i.e. the Clinical Supply Agreement).

8.3 Limitations on Indemnification. The obligations to indemnify, defend, and hold harmless set forth in this ARTICLE VIII (of the Clinical Supply Agreement) shall be contingent upon the Party seeking indemnification (the "Indemnitee"): (a) notifying the indemnifying Party of a claim, demand or suit in timely manner; provided, however, that Indemnitee's failure or delay in providing such notice shall not relieve the indemnifying Party of its indemnification obligation except to the extent the indemnifying Party is prejudiced thereby; (b) allowing the indemnifying Party or its insurers the right to assume direction and control of the defense of any claim, demand or suit; (c) using its best efforts to cooperate with the indemnifying Party or its insurers, at the indemnifying Party's expense, in the defense of such claim, demand or suit; and (d) not settling or compromising any claim, demand or suit without prior written authorization of the indemnifying Party (not to be unreasonably withheld). The indemnifying Party will act reasonably and in good faith with respect to all matters relating to such claim, demand or suit and will not settle or otherwise resolve such claim, demand or suit without the Indemnitee's prior written consent, which will not be unreasonably withheld, conditioned or delayed; provided that such consent will not be required with respect to any settlement involving only the payment of monetary awards for which the indemnifying Party will be fully-responsible. The Indemnitee shall have the right, at the Indemnitee's expense, to employ one separate counsel and to participate in the defense of such claim, demand or suit; provided that the indemnifying Party shall bear the reasonable fees, costs and expenses of one such separate counsel and participation if the Indemnitee shall have reasonably determined, after consultation with counsel, that an actual or potential conflict of interest makes representation by the same counsel or the counsel selected by the indemnifying Party inappropriate.

8.4 LIMITATION OF LIABILITY; RIGHT TO OFFSET.

(a) Consequential Damages Limitation. In no event will any Party be liable to the other Party for any indirect, special, incidental, exemplary or consequential damages of any kind arising out of or in connection with this Agreement (i.e. the Clinical Supply Agreement), however caused and on any theory of liability (whether in contract, tort (including negligence), strict liability or otherwise), even if such Party was advised or otherwise aware of the likelihood of such damages. The foregoing limitations will not apply with respect to (a) the Party's indemnification obligations under this Agreement (i.e. the Clinical Supply Agreement), (b) breach by a Party of ARTICLE X (Confidential Information) (of the Clinical Supply Agreement) or (c) intentional misconduct of a Party.

(b) Offset. Following the determination of Losses subject to indemnification under Section 8.1 (of the Clinical Supply Agreement) by Supplier or Section 8.2 (of the Clinical Supply Agreement) by Purchaser by a court of competent jurisdiction, the Indemnitee shall have a right to offset such Losses against any current or future payment due to the indemnifying Party hereunder or under the License Agreement. In addition, either Party shall have a right to offset any damages owed to it of any kind arising out of or in connection with this Agreement (i.e. the Clinical Supply Agreement), however caused and on any theory of liability (whether in contract, tort (including negligence), strict liability or otherwise, against any current or future payment to the other Party hereunder or under the License Agreement.

Exhibit 12.1

STATEMENT REGARDING COMPUTATION OF CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES AND RATIOS OF EARNINGS TO COMBINED FIXED CHARGES AND PREFERRED STOCK DIVIDENDS

	Fiscal Year Ended December 31,				
	2017	2016	2015	2014	2013
Loss from operations	(128,984)	(110,732)	(119,076)	(75,846)	(33,950)
add: Fixed charges (see below)	399	383	344	173	58
Pre-tax loss from continuing operations plus fixed charges	(128,585)	(110,349)	(118,732)	(75,673)	(33,892)
Fixed charges:					
Interest expense on indebtedness	—	—	—	—	—
Interest expense on portion of rent expense representative of interest	399	383	344	173	58
Total fixed charges	399	383	344	173	58
Ratio of earnings to fixed charges	—	—	—	—	—
Deficiency of earnings available to cover fixed charges	(128,984)	(110,732)	(119,076)	(75,846)	(33,950)

$ in thousands

Exhibit 21.1

Subsidiaries of Karyopharm Therapeutics Inc.

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

Exhibit 23.1

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 Statement (Form S-8, File No. 333-210221) 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. 333-214489) and related Prospectus of Karyopharm Therapeutics Inc. for the registration of debt securities, common stock, preferred stock, and warrants; and
5. Registration Statement (Form S-3, File No. 333-222726) and related Prospectus of Karyopharm Therapeutics Inc. for the registration of debt securities, common stock, preferred stock, warrants, and units;

of our report dated March 15, 2018, with respect to the consolidated financial statements of Karyopharm Therapeutics Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2017.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 15, 2018

Exhibit 31.1

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: March 15, 2018

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

Exhibit 31.2

I, Michael F. Falvey, 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: March 15, 2018

/s/ Michael F. Falvey

Michael F. Falvey
Executive Vice President, Chief Financial Officer and Treasurer

Exhibit 32.1

**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, 2017, 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: March 15, 2018

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

/s/ Michael F. Falvey
Michael F. Falvey
Executive Vice President, Chief Financial Officer and Treasurer